PCT

WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro

INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 :
C07D 295/12, A61K 31/50, C07D 403/04, 317/58, 207/06, 215/06, 215/24, 217/04, 213/70, 213/30, C07C 237/32, 311/08, 311/21

A1

(11) Internationale Veröffentlichungsnummer: WO 99/54320

(43) Internationales Veröffentlichungsdatum: 28. Oktober 1999 (28.10.99)

(21) Internationales Aktenzeichen: PCT/EP99/02620

(22) Internationales Anmeldedatum: 19. April 1999 (19.04.99)

(30) Prioritätsdaten:
198 17 460.8 20. April 1998 (20.04.98) DE

(71) Anmelder (*für alle Bestimmungsstaaten ausser US*): BASF AKTIENGESELLSCHAFT [DE/DE]; D-67056 Ludwigshafen (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder (*nur für US*): LUBISCH, Wilfried [DE/DE]; Häusererstrasse 15, D-69115 Heidelberg (DE). MÖLLER, Achim [DE/DE]; Im Zaunrücken 10, D-67269 Grünstadt (DE). TREIBER, Hans-Jörg [DE/DE]; Sperberweg 1, D-68782 Brühl (DE). KNOPP, Monika [DE/DE]; Karl-Dillinger-Strasse 19, D-67071 Ludwigshafen (DE).

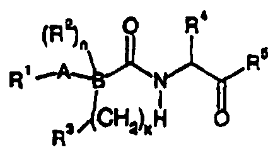
(74) Gemeinsamer Vertreter: BASF AKTIENGESELLSCHAFT; D-67056 Ludwigshafen (DE).

(81) Bestimmungsstaaten: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, ZA, eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: NOVEL HETEROCYCLICALLY SUBSTITUTED AMIDES WITH CYSTEINE PROTEASE-INHIBITING EFFECT

(54) Bezeichnung: NEUE HETEROCYCLISCH SUBSTITUIERTE AMIDE MIT CYSTEIN-PROTEASE HEMMENDER WIRKUNG



(I)

(57) Abstract

The invention relates to amides of the general formula (I), which are inhibitors of enzymes, especially cysteine proteases.

(57) Zusammenfassung

Die Erfindung betrifft Amide der allgemeinen Formel (I), die Inhibitoren von Enzymen, insbesondere Cystein-Proteasen darstellen.

104.

NEUE HETEROCYCLISCH SUBSTITUIERTE AMIDE MIT CYSTEIN-PROTEASE HEMMENDER WIRKUNG

Beschreibung

Die vorliegende Erfindung betrifft neuartige Amide, die Inhibitoren von Enzymen, insbesondere Cystein-Proteasen, wie Calpain (= Calcium dependant cysteine proteases) und dessen Isoenzyme und Cathepsine, zum Beispiel B und L, darstellen.

Calpaine stellen intracelluläre, proteolytische Enzyme aus der Gruppe der sogenannten Cystein-Proteasen dar und werden in vielen Zellen gefunden. Calpaine werden durch erhöhte Kalziumkonzentration aktiviert, wobei man zwischen Calpain I oder µ-Calpain, das durch µ-molare Konzentrationen von Calzium-Ionen aktiviert wird, und Calpain II oder m-Calpain, das durch m-molare Konzentrationen von Kalzium-Ionen aktiviert wird, unterscheidet (P.Johnson, Int.J.Biochem. 1990, *22(8)*, 811-22). Heute werden noch weitere Calpain-Isoenzyme postuliert (K.Suzuki et al., Biol.Chem. Hoppe-Seyler, 1995, *376(9)*,523-9).

Man vermutet, daß Calpaine in verschiedenen physiologischen Prozessen eine wichtige Rolle spielen. Dazu gehören Spaltungen von regulatorischen Proteinen wie Protein-Kinase C, Cytoskelett-Proteine wie MAP 2 und Spektrin, Muskelproteine, Proteinabbau in rheumatoider Arthritis, Proteine bei der Aktivierung von Plättchen, Neuropeptid-Metabolismus, Proteine in der Mitose und weitere, die in M.J.Barrett et al., Life Sci. 1991, *48*, 1659-69 und K.K.Wang et al., Trends in Pharmacol.Sci., 1994, *15*, 412-9 aufgeführt sind.

Bei verschiedenen pathophysiologischen Prozessen wurden erhöhte Calpain-Spiegel gemessen, zum Beispiel: Ischämien des Herzens (z.B. Herzinfarkt), der Niere oder des Zentralnervensystems (z.B. "Stroke"), Entzündungen, Muskeldystrophien, Katarakten der Augen, Verletzungen des Zentralnervensystems (z.B. Trauma), Alzheimer Krankheit usw.(siehe K.K. Wang, oben). Man vermutet einen Zusammenhang dieser Krankheiten mit erhöhten und anhaltenden intrazellulären Kalziumspiegeln. Dadurch werden Kalzium-abhängige Prozesse überaktiviert und unterliegen nicht mehr der physiologischen Regelung. Dementsprechend kann eine Überaktivierung von Calpainen auch pathophysiologische Prozesse auslösen.

Daher wurde postuliert, daß Inhibitoren der Calpain-Enzyme für die Behandlung dieser Krankheiten nützlich sein können. Verschiedene Untersuchungen bestätigen dies. So haben Seung-Chyul Hong et

al., Stroke 1994, *25(3)*, 663-9 und R.T.Bartus et al., Neurological Res. 1995, *17*, 249-58 eine neuroprotektive Wirkung von Calpain-Inhibitoren in akuten neurodegenerativen Störungen oder Ischämien, wie sie nach Hirnschlag auftreten, gezeigt. Ebenso nach experimentellen Gehirntraumata verbesserten Calpain-Inhibitoren die Erholung der auftretenden Gedächtnisleistungsdefizite und neuromotorischen Störungen (K.E.Saatman et al. Proc.Natl. Acad.Sci. USA, 1996, *93*,3428-3433). C.L.Edelstein et al., Proc.Natl.Acad.Sci. USA, 1995, *92*, 7662-6, fand eine protektive Wirkung von Calpain-Inhibitoren auf durch Hypoxie geschädigten Nieren. Yoshida, Ken Ischi et al., Jap.Circ.J. 1995, *59(1)*, 40-8, konnten günstige Effekte von Calpain-Inhibitoren nach cardialen Schädigungen aufzeigen, die durch Ischämie oder Reperfusion erzeugt wurden. Da Calpain-Inhibitoren die Freisetzung von dem β-AP4-Protein hemmen, wurde eine potentielle Anwendung als Therapeutikum der Alzheimer Krankheit vorgeschlagen (J.Higaki et al., Neuron, 1995, *14*, 651-59). Die Freisetzung von Interleukin-1α wird ebenfalls durch Calpain-Inhibitoren gehemmt (N.Watanabe et al., Cytokine 1994, *6(6)*, 597-601). Weiterhin wurde gefunden, daß Calpain-Inhibitoren cytotoxische Effekte an Tumorzellen zeigen (E.Shiba et al. 20th Meeting Int.Ass.Breast Cancer Res., Sendai Jp, 1994, 25.-28.Sept., Int.J.Oncol. *5(Suppl.)*, 1994, 381).

Weitere mögliche Anwendungen von Calpain-Inhibitoren sind in K.K.Wang, Trends in Pharmacol.Sci., 1994, *15*, 412-8, aufgeführt.

Calpain-Inhibitoren sind in der Literatur bereits beschrieben worden. Überwiegend sind dies jedoch entweder irreversible oder peptidische Inhibitoren. Irreversible Inhibitoren sind in der Regel alkylierende Substanzen und haben den Nachteil, daß sie im Organismus unselektiv reagieren oder instabil sind. So zeigen diese Inhibitoren oft unerwünschte Nebeneffekte, wie Toxizität, und sind danach in der Anwendung eingeschränkt oder nicht brauchbar. Zu den irreveriblen Inhibitoren kann man zum Beispiel die Epoxide E 64 (E.B.McGowan et al., Biochem.Biophys.Res.Commun. 1989, *158*, 432-5), α-Halogenketone (H.Angliker et al., J.Med.Chem. 1992, *35*, 216-20) oder Disulfide (R.Matsueda et al., Chem.Lett. 1990, 191-194) zählen.

Viele bekannte reversible Inhibitoren von Cystein-Proteasen wie Calpain stellen peptidische Aldehyde dar, insbesondere dipeptidische und tripepidische Aldehyde wie zum Beispiel Z-Val-Phe-H (MDL 28170) (S.Mehdi, Tends in Biol.Sci. 1991, *16*, 150-3). Unter physiologischen Bedingungen haben peptidische Aldehyde den Nachteil, daß sie auf Grund der großen Reaktivität häufig insta-

bil sind, schnell metabolisiert werden können und zu unspezifischen Reaktionen neigen, die die Ursache von toxischen Effekten sein können (J.A.Fehrentz und B.Castro, Synthesis 1983, 676-78. In JP 08183771 (CA 1996, 605307) und in EP 520336 sind Aldehyde, die sich von 4-Piperidinoylamide und 1-Carbonyl-piperidino-4-ylamide ableiten als Calpain-Inhibitoren beschrieben worden. Jedoch sind die hier beanspruchten Aldehyde, die sich von heteroaromatisch substituierten Amiden der allgemeinen Struktur I ableiten bisher noch beschrieben worden.

Peptidische Keton-Derivate sind ebenfalls Inhibitoren von Cystein-Proteasen, insbesondere Calpaine. So sind zum Beispiel bei Serin-Proteasen Keton-Derivate als Inhibitoren bekannt, wobei die Keto-Gruppe von einer elektronenziehenden Gruppe wie CF_3 aktiviert wird. Bei Cystein-Proteasen sind Derivate mit durch CF_3 oder ähnlichen Gruppen aktivierte Ketone wenig oder nicht wirksam (M.R.Angelastro et al., J.Med.Chem. 1990,*33*, 11-13). Überraschenderweise konnten bei Calpain bisher nur Keton-Derivate, bei denen einerseits α-ständige Abgangsgruppen eine irreversible Hemmung verursachen und andererseits ein Carbonsäure-Derivat die Keto-Gruppe aktiviert, als wirksame Inhibitoren gefunden werden (siehe M.R.Angelastro et al., siehe oben; WO 92/11850; WO 92,12140; WO 94/00095 und WO 95/00535). Jedoch sind von diesen Ketoamiden und Ketoestern bisher nur peptidische Derivate als wirksam beschrieben worden (Zhaozhao Li et al., J.Med.Chem. 1993, *36*, 3472-80; S.L.Harbenson et al., J.Med.Chem. 1994, *37*, 2918-29 und siehe oben M.R.Angelastro et al.).

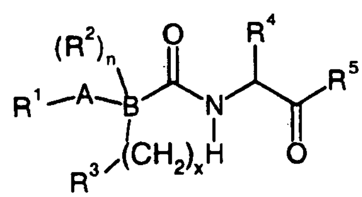
Ketobenzamide sind bereits in der Literatur bekannt. So wurde der Ketoester $PhCO-Abu-COOCH_2CH_3$ in WO 91/09801, WO 94/00095 und 92/11850 beschrieben. Das analoge Phenyl-Derivat $Ph-CONH-CH(CH_2Ph)-CO-COCOOCH_3$ wurde in M.R.Angelastro et al., J.Med.Chem. 1990,*33*, 11-13 als jedoch nur schwacher Calpain-Inhibitor gefunden. Dieses Derivat ist auch in J.P.Burkhardt, Tetrahedron Lett., 1988, 3433-36 beschrieben. Die Bedeutung der substituierten Benzamide ist jedoch bisher nie untersucht worden.

In einer Reihe von Therapien wie Schlaganfall werden die Wirkstoffe intravenös zum Beispiel als Infusionslösung appliziert. Dazu ist es notwendig, Substanzen, hier Calpain-Inhibitoren, zur Verfügung zu haben, die ausreichende Wasserlöslichkeit aufweisen, so daß eine Infusionslösung hergestellt werden kann. Viele der beschriebenen Calpain-Inhibitoren haben jedoch den Nachteil, daß sie nur geringe oder keine Wasserlöslichkeit zeigen und somit nicht für eine intravenöse Applikation in Frage kommen. Derartige Wirkstoffe können nur mit Hilfsstoffen, die die Wasserlöslichkeit vermitteln sollen, appliziert werden (vgl. R.T. Bartus et al. J

Cereb. Blood Flow Metab. 1994, *14*, 537-544). Diese Hilfsstoffe, zum Beispiel Polyethylenglykol, haben aber häufig Begleiteffekte oder sind sogar unverträglich. Ein nicht-peptidischer Calpain-Inhibitor, der also ohne Hilfsstoffe wasserlöslich ist, hätte somit einen großen Vorteil. Ein solcher Inhibitor ist bisher nicht beschrieben worden und wäre damit neu.

In der vorliegenden Erfindung wurden substituierte nicht-peptidische Aldehyde, Ketocarbonsäureester und Ketoamid-Derivate beschrieben. Diese Verbindungen sind neu und zeigen überraschenderweise die Möglichkeit auf, durch Einbau von rigiden strukturellen Fragmenten potente nicht-peptidische Inhibitoren von Cystein-Proteasen, wie z.B. Calpain, zu erhalten. Weiterhin sind bei den vorliegenden Verbindungen der allgemeinen Formel I, die alle mindestens ein aliphatischen Amin-Rest tragen Salz-Bindungen mit Säuren möglich. Eine Vielzahl dieser Substanzen zeigen als 0.5 %ige Lösung Wasserlöslichkeit bei pH 0 4-5 und damit zeigen sie das gewünschte Profil für eine intravenöse Applikation, wie sie zum Beispiel bei der Schlaganfall-Therapie erforderlich ist.

Gegenstand der vorliegenden Erfindung sind Amide der allgemeinen Formel I

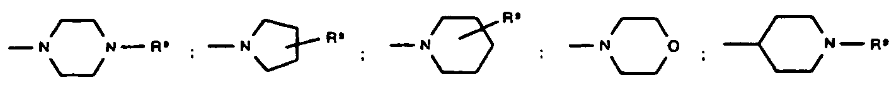


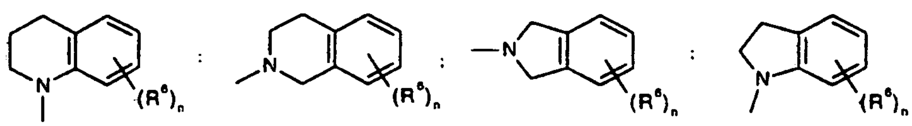
und ihre tautomeren und isomeren Formen, möglichen enantiomeren und diastereomeren Formen, sowie mögliche physiologisch verträgliche Salze, worin die Variablen folgende Bedeutung haben:

R^1 Wasserstoff, C_1-C_6-Alkyl, verzweigt und unverzweigt, Phenyl, Naphthyl, Chinolinyl, Pyridyl, Pyrimidyl, Pyrazyl, Pyridazyl, Chinazolyl, Chinoxalyl, Thienyl, Benzothienyl, Benzofuranyl, Furanyl, und Indolyl bedeuten kann, wobei die Ringe noch mit zu bis 3 Resten R^6 substituiert sein können, und

R^2 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, O-C_1-C_6-Alkyl, verzweigt oder unverzweigt, C_2-C_6-Alkenyl, C_2-C_6-Alkinyl, C_1-C_6-Alkyl-Phenyl, C_2-C_6-Alkenyl-Phenyl, C_2-C_6-Alkinyl-Phenyl, OH, Cl, F, Br, J, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-Alkyl, NHCO-C_1-C_4-Alkyl, NHCO-Phenyl, $CONHR^9$, $NHSO_2$-C_1-C_4-Alkyl, $NHSO_2$-Phenyl, SO_2-C_1-C_4-Alkyl und SO_2-Phenyl bedeuten und

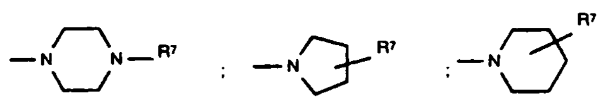
R^3 NR^7R^8 oder einen Ring darstellen kann wie





R^4 $-C_1$-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Phenyl-, Pyridyl- oder Naphthyl-Ring tragen kann, der seinerseits mit maximal zwei Resten R^6 substituiert ist, und

R^5 Wasserstoff, $COOR^{11}$ und CO-Z bedeutet, worin Z $NR^{12}R^{13}$ und



bedeutet und

R^6 Wasserstoff, C_1-C_4-Alkyl, verzweigt oder unverzweigt, $-O-C_1$-C_4- Alkyl, OH, Cl, F, Br, J, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-Alkyl, -NHCO-C_1-C_4-Alkyl, -NHCO-Phenyl, $-NHSO_2$-C_1-C_4-Alkyl, $-NHSO_2$-Phenyl, $-SO_2$-C_1-C_4-Alkyl und $-SO_2$-Phenyl bedeutet und

R^7 Wasserstoff, C_1-C_6-Alkyl, geradlinig oder verzweigt, bedeutet und das mit einem Phenylring substituiert kann, der selbst noch mit einem oder zwei Resten R^{10} substituiert sein kann, und

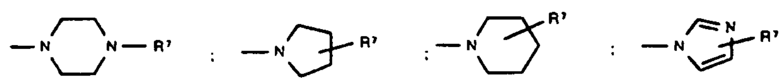
R^8 Wasserstoff, C_1-C_6-Alkyl, geradlinig oder verzweigt, bedeutet und das mit einem Phenylring substituiert kann, der selbst noch mit einem oder zwei Resten R^{10} substituiert sein kann, und

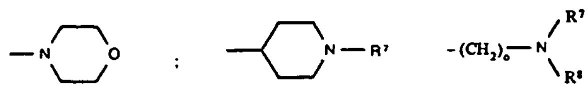
R^9 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Substituenten R^{16} tragen kann, Phenyl, Pyridyl, Pyrimidyl, Pyridazyl, Pyrazinyl, Pyrazyl, Naphthyl, Chinolinyl, Imidazolyl, das noch einen oder zwei Substituenten R^{14} tragen kann, und

R^{10} Wasserstoff, C_1-C_4-Alkyl, verzweigt oder unverzweigt, $-O-C_1$-C_4-Alkyl, OH Cl, F, Br, J, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-Alkyl, -NHCO-C_1-C_4-Alkyl, -NHCO-Phenyl, $-NHSO_2$-C_1-C_4-Alkyl, $-NHSO_2$-Phenyl, $-SO_2$-C_1-C_4-Alkyl und $-SO_2$-Phenyl bedeuten kann

R^{11} Wasserstoff, C_1-C_6-Alkyl, geradlinig oder verzweigt, bedeutet und das mit einem Phenylring substituiert kann, der selbst noch mit einem oder zwei Resten R^{10} substituiert sein kann, und

R^{12} Wasserstoff, C_1-C_6-Alkyl, verzweigt und unverzweigt, bedeutet, und





R^{13} Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch mit einem Phenylring, der noch einen Rest R^{10} tragen kann, und mit

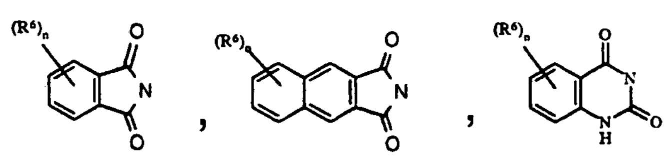
substituiert sein kann bedeutet, und

R^{14} Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, O-C_1-C_6-Alkyl, verzweigt oder unverzweigt, OH, Cl, F, Br, J, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-Alkyl bedeutet oder zwei Reste R^{14} eine Brücke $OC(R^{15})_2O$ darstellen kann und

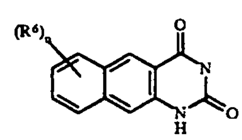
R^{15} Wasserstoff, C_1-C_6-Alkyl, verzweigt und unverzweigt, bedeutet und

R^{16} ein Phenyl-, Pyridyl-, Pyrimidyl-, Pyridazyl-, Pyrazinyl-, Pyrazyl-, Pyrrolyl-, Naphthyl-, Chinolinyl-, Imidazolyl-Ring sein kann, der noch einen oder zwei Substituenten R^6 tragen kann, und

A $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-(CH_2)_o-SO-(CH_2)_m-$, $-(CH_2)_o-SO_2-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$, $-CO-CH=CH-$, $-(CH_2)_o-CO-(CH_2)_m-$, $-(CH_2)_m-NHCO-(CH_2)_o-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-NHSO_2-(CH_2)_o-$, $-NH-CO-CH=CH-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$, $-CH=CH-CONH-$ und bedeutet,



und



R^1-A zusammen auch

bedeuten und

B Phenyl, Pyridin, Pyrimidin, Pyrazin, Imidazol und Thiazol bedeutet und

x 1, 2 oder 3 und

n eine Zahl 0, 1 oder 2 bedeutet,und

m, o unabhängig voneinander eine Zahl 0, 1, 2, 3 oder 4 bedeutet.

Die Verbindungen der Formel I können als Racemate, als enantiomerenreine Verbindungen oder als Diastereomere eingesetzt werden. Werden enantiomerereine Verbindungen gewünscht, kann man diese beispielsweise dadurch erhalten, daß man mit einer geeigneten optisch aktiven Base oder Säure eine klassische Racematspaltung mit den Verbindungen der Formel I oder ihren Zwischenprodukten durchführt. Andererseits können die enantiomeren Verbindungen ebenfalls durch Einsatz von kommerziell erwerbbaren Verbindungen, zum Beispiel optisch aktiven Aminosäuren wie Phenylalanin, Tryptophan und Tyrosin, hergestellt werden.

Gegenstand der Erfindung sind auch zu Verbindungen der Formel I mesomere oder tautomere Verbindungen, beispielsweise solche, bei denen die Aldehyd- oder Ketogruppe der Formel I als Enol-Tautomeres vorliegt.

Ein weiterer Gegenstand der Erfindung sind die physiologisch verträglichen Salze der Verbindungen I, die sich durch Umsatz von Verbindungen I mit einer geeigneten Säure oder Base erhalten lassen. Geeignete Säuren und Basen sind zum Beispiel in Fortschritte der Arzneimittelforschung, 1966, Birkhäuser Verlag, Bd.10, S. 224-285, aufgelistet. Dazu zählen zum Beispiel Salzsäure, Citronensäure, Weinsäure, Milchsäure, Phosphorsäure, Methansulfonsäure, Essigsäure, Ameisensäure, Maleinsäure, Fumarsäure usw. bzw. Natriumhydroxid, Lithiumhydroxid,. Kaliumhydroxid und Tris.

Die Herstellung der erfindungsgemäßen Amide I kann auf verschiedenen Wegen erfolgen, die im Syntheseschema skizziert wurde.

Syntheseschema

Heterocyclische Karbonsäuren II werden mit geeigneten Aminoalkoholen III zu den entsprechenden Amiden IV verknüpft. Dabei benutzt man übliche Peptid-Kupplungs-Methoden, die entweder im C.R.Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, Seite 972f. oder im Houben-Weyl, Methoden der organischen Chemie, 4.Aufl., E5, Kap.V aufgeführt sind. Bevorzugt arbeitet

man mit "aktivierten" Säurederivaten von II, wobei die Säuregruppe COOH in eine Gruppe COL überführt wird. L stellt eine Abgangsgruppe wie zum Beispiel Cl, Imidazol und N-Hydroxybenzotriazol dar. Diese aktivierte Säure wird anschließend mit Aminen zu den Amiden IV umgesetzt. Die Reaktion erfolgt in wasserfreien, inerten Lösungsmitteln wie Methylenchlorid, Tetrahydrofuran und Dimethylformamid bei Temperaturen von -20 bis +25°C.

Diese Alkohol-Derivate IV können zu den erfindungsgemäßen Aldehyd-Derivaten I oxidiert werden. Dafür kann man verschiedene übliche Oxidationsreaktionen (siehe C.R.Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, Seite 604 f.) wie zum Beispiel Swern- und Swern-analoge Oxidationen (T.T.Tidwell, Synthesis 1990, 857-70), Natriumhypochlorid/TEMPO (S.L.Harbenson et al., siehe oben) oder Dess-Martin (J.Org.Chem. 1983, 48, 4155) benutzen. Bevorzugt arbeitet man hier in inerten aprotischen Lösungsmitteln wie Dimethylformamid, Tetrahydrofuran oder Methylenchorid mit Oxidationsmitteln wie DMSO/ py x SO_3 oder DMSO/ Oxalylchorid bei Temperaturen von -50 bis +25°C, je nach Methode (siehe obige Literatur).

Alternativ kann man die Karbonsäure II mit Aminohydroxamsäure-Derivate VI zu Benzamiden VII umsetzten. Dabei bedient man sich der gleichen Reaktionsführung wie bei der Darstellung von IV. Die Hydroxam-Derivate VI sind aus den geschützten Aminosäuren V durch Umsatz mit einem Hydroxylamin erhältlich. Dabei benutzt auch hier ein bereits beschriebenes Amidherstellungsverfahren. Die Abspaltung der Schutzgruppe X, zum Beispiel Boc, erfolgt in üblicherweise, zum Beispiel mit Trifluoressigsäure. Die so erhaltenen Amid-hydroxamsäuren VII können durch Reduktion in die erfindungsgemäßen Aldehyde I umgewandelt werden. Dabei benutzt man zum Beispiel Lithiumaluminiumhydrid als Reduktionsmittel bei Temperaturen von -60 bis 0°C in inerten Lösungsmitteln wie Tetrahydrofuran oder Ether.

Analog zum letzten Verfahren kann man auch Karbonsäuren oder Säure-Derivate, wie Ester IX (Y = COOR', COSR') herstellen, die ebenfalls durch Reduktion in die erfindungsgemäßen Aldehyde I überführt werden können. Diese Verfahren sind in R.C.Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, Seite 619-26 aufgelistet.

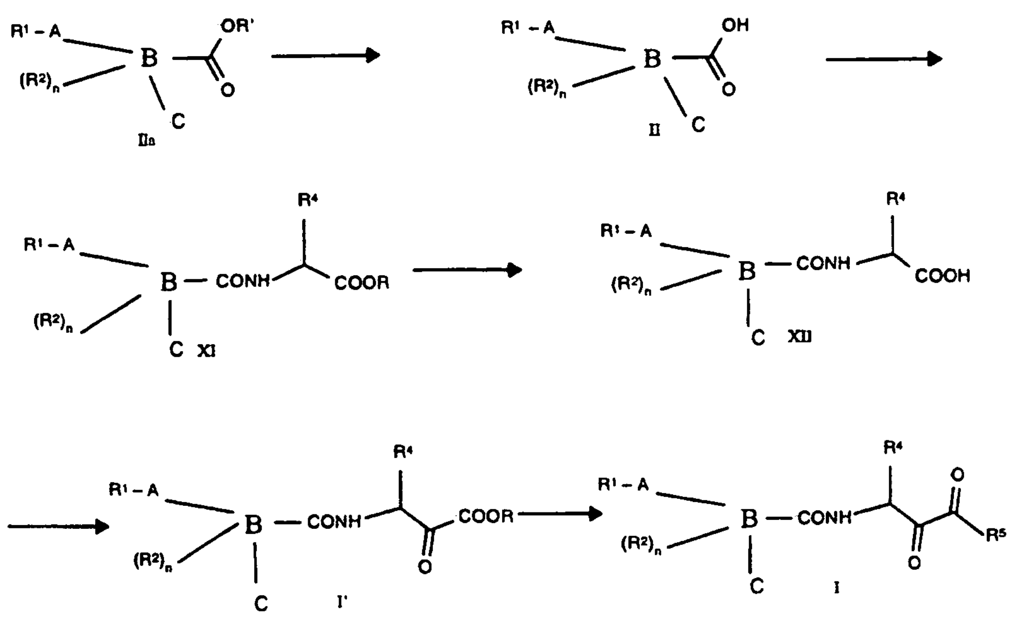
Die Herstellung der erfindungsgemäßen heterozyklisch substituierten Amide I, eine Ketoamid- oder Ketoester-gruppe tragen, kann auf verschiedenen Wegen erfolgen, die in den Syntheseschemata 2 und 3 skizziert wurden.

Gegebenenfalls werden die Karbonsäureester IIa mit Säuren oder Basen wie Lithiumhydroxid, Natriumhydroxid oder Kaliumhydroxid in wäßrigen Medium oder in Gemischen aus Wasser und organischen Lösungsmitteln wie Alkohole oder Tetrahydrofuran bei Raumtemperatur oder erhöhten Temperaturen, wie 25-100°C, in die Säuren II überführt.

Diese Säuren II werden mit einem α-Aminosäure-Derivat verknüpft, wobei man übliche Bedingungen benutzt, die zum Beispiel im Houben-Weyl, Methoden der organischen Chemie, 4.Aufl., E5, Kap. V, und C.R.Larock, Comprehensive Organic Transformations, VCH Publisher, **1989**, *Ch.9* aufgelistet sind.

Zum Beispiel werden die Carbonsäuren II in die "aktivierten" Säure-Derivate IIb =Y-COL überführt, wobei L eine Abgangsgruppe wie Cl, Imidazol und N-Hydroxybenzotriazol darstellt und anschließend durch Zugabe von einem Aminosäure-Derivat H_2N-CH(R^3)-COOR in das Derivat XI überführt. Diese Reaktion erfolgt in wasserfreien, inerten Lösungsmitteln wie Methylenchlorid, Tetrahydrofuran und Dimethylformamid bei Temperaturen von -20 bis +25°C.

Schema 1



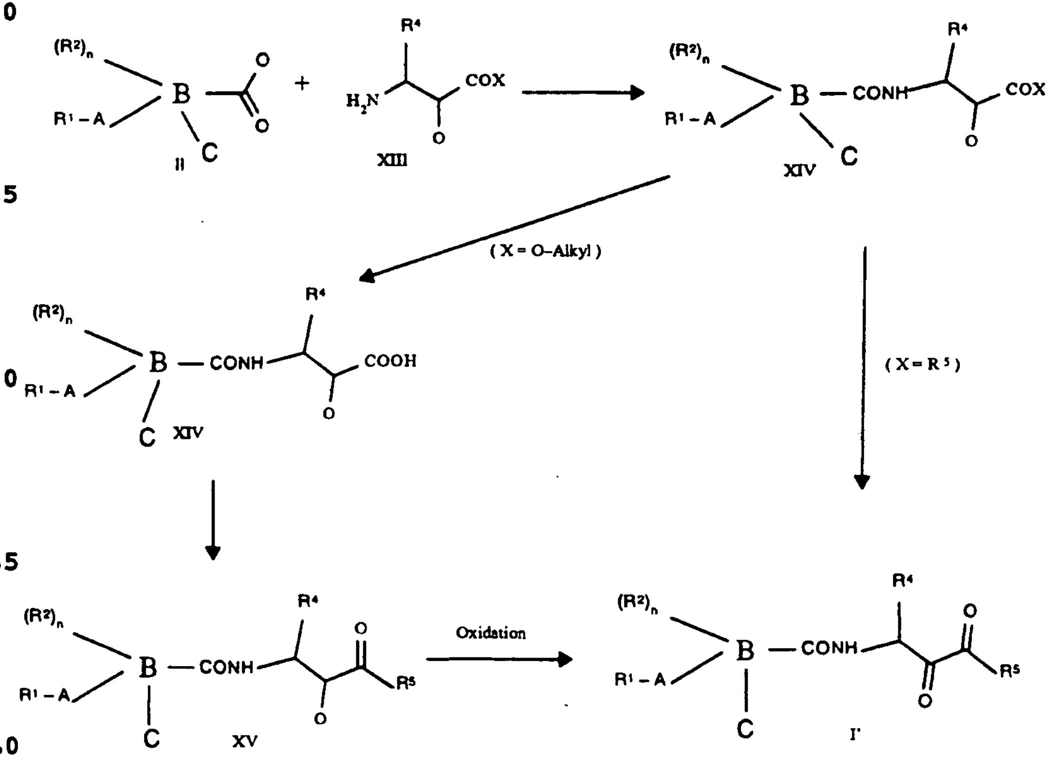
C = R^3–(CH_2)$_x$–

Die Derivate XI, die in der Regel Ester darstellen, werden analog der oben beschriebenen Hydrolyse in die Ketokarbonsäuren XII überführt. In einer Dakin-West analogen Reaktion werden die Ketoester I' hergestellt, wobei nach einer Methode von ZhaoZhao Li et

al.. J.Med.Chem., 1993, *36*, 3472-80 gearbeitet wird. Dabei werden eine Karbonsäuren wie XII bei erhöhter Temperatur (50-100°C) in Lösungsmitteln, wie zum Beispiel Tetrahydrofuran, mit Oxalsäure-monoesterchlorid umgesetzt und anschließend das so erhaltene Produkt mit Basen wie Natriumethanolat in Ethanol bei Temperaturen von 25-80°C zum erfindungsgemäßen Ketoester I' umgesetzt. Die Ketoester I' können, wie oben beschrieben, zum Beispiel zu erfindungsgemäßen Ketocarbonsäuren hydrolysiert werden.

Die Umsetzung zu Ketobenzamiden I' erfolgt ebenfalls analog der Methode von ZhaoZhao Li et al.(s.oben). Die Ketogruppe in I' wird durch Zugabe von 1,2-Ethandithiol unter Lewissäure-Katalyse, wie zum Beispiel Bortrifluoridetherat, in inerten Lösungsmitteln, wie Methylenchlorid, bei Raumtemperatur geschützt, wobei ein Dithian anfällt. Diese Derivate werden mit Aminen R^3-H in polaren Lösungsmitteln, wie Alkohole, bei Temperaturen von 0-80°C umgesetzt, wobei die Ketoamide I (R^4 =Z oder NR^7R^8) anfallen.

Schema 2



C = $R^3-(CH_2)_x-$

Eine alternative Methode ist im Schema 2 dargestellt. Die Ketokarbonsäuren II werden mit Aminohydroxykarbonsäure-Derivaten XIII (Herstellung von XIII siehe S.L.Harbenson et al., J.Med.Chem. 1994, *37*,2918-29 oder J.P. Burkhardt et al. Tetrahedron Let.

1988, 29, 3433-3436) unter üblichen Peptid-Kupplungs-Methoden (siehe oben, Houben-Weyl) umgesetzt, wobei Amide XIV anfallen. Diese Alkohol-Derivate XIV können zu den erfindungsgemäßen Ketokarbonsäure-Derivaten I oxidiert werden. Dafür kann man verschiedene übliche Oxidationsreaktionen (siehe C.R.Larock, Comprehensive Organic Transformations, VCH Publisher, Seite 604 f.) wie zum Beispiel Swern- und Swern-analoge Oxidationen, bevorzugt Dimethylsulfoxid/ Pyridin-Schwefeltrioxid-Komplex in Lösungsmitteln wie Methylenchorid oder Tetrahydrofuran, gegebenenfalls unter Zusatz von Dimethylsulfoxid, bei Raumtemperatur oder Temperaturen von -50 bis 25°C, (T.T.Tidwell, Synthesis 1990, 857-70) oder Natriumhypochlorid/TEMPO (S.L.Harbenson et al., siehe oben), benutzen.

Wenn XIV α-Hydroxyester darstellen (X = O-Alkyl), können diese zu Karbonsäuren XV hydrolysiert werden, wobei analog zu den obigen Methoden gearbeitet wird, bevorzugt aber mit Lithiumhydroxid in Wasser/Tetrahydrofuran-Gemischen bei Raumtemperatur. Die Herstellung von anderen Estern oder Amiden XVI erfolgt durch Umsetzung mit Alkoholen oder Aminen unter bereits beschriebenen Kupplungsbedingungen. Das Alkohol-Derivat XVI kann erneut zu erfindungsgemäßen Ketokarbonsäure-Derivaten I oxidiert werden.

Die Herstellung der Karbonsäureester II sind teilweise bereits beschrieben worden oder erfolgt entsprechend üblicher chemischen Methoden.

Verbindungen, bei denen X eine Bindung darstellt, werden durch übliche aromatische Kupplung, zum Beispiel die Suzuki-Kupplung mit Borsäure-Derivaten und Halogenide unter Palladiumkatalyse oder Kupferkatalytische Kupplung von aromatischen Halogeniden, hergestellt. Die Alkyl-überbrückten Reste (X= $-(CH_2)_m-$) können durch Reduktion der analogen Ketone oder durch Alkylierung der Organolithium , z.B. ortho-Phenyloxazolidine, oder anderer Organometallverbindungen hergestellt werden (vgl. I.M.Dordor, et al., J.Chem.Soc. Perkin Trans. I, 1984, 1247-52).

Ether-überbrückte Derivate werden durch Alkylierung der entsprechenden Alkohole oder Phenole mit Halogeniden hergestellt.

Die Sulfoxide und Sulfone sind durch Oxidation der entsprechenden Thioether zugänglich.

Alken- und Alkin- überbrückte Verbindungen werden zum Beispiel durch Heck-Reaktion aus aromatischen Halogeniden und entsprechenden Alkenen und Alkinen hergestellt (vgl. I.Sakamoto et al., Chem.Pharm.Bull., 1986, *34*, 2754-59).

Die Chalkone entstehen durch Kondensation aus Acetophenonen mit Aldehyden und können gegebenenfalls durch Hydrierung in die analogen Alkyl-Derivate überführt werden..

Amide und Sulfonamide werden analog den oben beschriebenen Methoden aus den Aminen und Säure-Derivaten hergestellt.

Die Dialkylaminoalkylsubstituenten werden durch reduktive Aminierung der Aldehydderivate mit den entsprechenden Aminen in Gegenwart von Borhydriden , wie BH_3-Pyridin-Komplex oder oder $NaBH_3CN$ erhalten (A:F:Abdel-Magid, C:A:Maryanoff, K.G. Carson, Tetrahedron Lett. 10990, 31, 5595; A.E: Moormann, Synth. Commun. 1993, 23, 789).

Die in der vorliegenden Erfindung enthaltenen heterozyklisch substituierte Amide I stellen Inhibitoren von Cystein-Proteasen dar, insbesondere Cystein-Proteasen wie die Calpaine I und II und Cathepsine B bzw. L.

Die inhibitorische Wirkung der heterozyklisch substituierte Amide I wurde mit in der Literatur üblichen Enzymtests ermittelt, wobei als Wirkmaßstab eine Konzentration des Inhibitors ermittelt wurde, bei der 50% der Enzymaktivität gehemmt wird (= IC_{50}). Die Amide I wurden in dieser Weise auf Hemmwirkung von Calpain I, Calpain II und Cathepsin B gemessen.

Cathepsin B-Test

Die Cathepsin B-Hemmung wurde analog einer Methode von S.Hasnain et al., J.Biol.Chem. 1993, *268*, 235-40 bestimmt.

Zu 88µL Cathepsin B (Cathepsin B aus menschlicher Leber (Calbiochem), verdünnt auf 5 Units in 500µM Puffer) werden 2µL einer Inhibitor-Lösung, hergestellt aus Inhibitor und DMSO (Endkonzentrationen: 100µM bis 0,01µM). Dieser Ansatz wird für 60 Minuten bei Raumtemperatur (25°C) vorinkubiert und anschließend die Reaktion durch Zugabe von 10µL 10mM Z-Arg-Arg-pNA (in Puffer mit 10% DMSO) gestartet. Die Reaktion wird 30 Minuten bei 405nM im Mikrotiterplattenreader verfolgt. Aus den maximalen Steigungen werden anschließend die IC_{50}'s bestimmt.

Calpain I und II Test

Die Testung der inhibitorischen Eigenschaften von Calpain-Inhibitoren erfolgt in Puffer mit 50 mM Tris-HCl, pH 7,5 ; 0,1 M NaCl; 1 mM Dithiotreithol; 0,11 mM Ca Cl_2, wobei das fluorogene Calpainsubstrats Suc-Leu-Tyr-AMC (25 mM gelöst in DMSO, Bachem/Schweiz) verwendet wird. Humanes µ-Calpain wird aus Erythrozyten isoliert und nach mehren chromatographischen Schritten (DEAE-Sepharose, Phenyl-Sepharose, Superdex 200 und Blue-Sepharose) erhält man Enzym mit einer Reinheit >95%, beurteilt nach SDS-PAGE, Western Blot Analyse und N-terminaler Sequenzierung. Die Fluoreszenz des Spaltproduktes 7-Amino-4-methylcoumarin (AMC) wird in einem Spex-Fluorolog Fluorimeter bei λex = 380 nm und λem = 460 nm verfolgt. In einem Meßbereich von 60 min. ist die Spaltung des Substrats linear und die autokatalytische Aktivität von Calpain gering, wenn die Versuche bei Temperaturen von 12° C durchgeführt werden. Die Inhibitoren und das Calpainsubstrat werden in den Versuchsansatz als DMSO-Lösungen gegeben,, wobei DMSO in der Endkonzentration 2% nicht überschreiten soll.

In einem Versuchsansatz werden 10 µl Substrat (250µM final) und anschließend 10 µl an µ-Calpain (2µg/ml final, d.h.18 nM) in eine 1 ml Küvette gegeben, die Puffer enthält. Die Calpain-vermittelte Spaltung des Substrats wird für 15 - 20 min. gemessen. Anschließend Zugabe von 10 µl Inhibitor (50 - 100 µM Lösung in DMSO) und Messung der Inhibition der Spaltung für weitere 40 min.

K_i -Werte werden nach der klassischen Gleichung für reversible Hemmung bestimmt:

(Methods in Enzymology,)

Ki = I / (v0/vi) - 1 ; wobei I= Inhibitorkonzentration, v0 = Anfangsgeschwindigkeit vor Zugabe des Inhibitors; vi = Reaktionsgeschwindigkeit im Gleichgewicht.

Die Geschwindigkeit wird errechnet aus v = Freisetzung AMC/ Zeit d.h. Höhe /Zeit.

Calpain ist eine intrazelluläre Cysteinprotease. Calpain-Inhibitoren müssen die Zellmembran passieren, um den Abbau von intrazellulären Proteinen durch Calpain zu verhindern. Einige bekannte Calpain-Inhibitoren, wie zum Beispiel E 64 und Leupeptin, überwinden die Zellmembranen nur schlecht und zeigen dementsprechend, obwohl sie gute Calpain-Inhibitoren darstellen, nur schlechte Wirkung an Zellen. Ziel ist es, Verbindungen mit besser Membran-

gängigkeit zu finden. Als Nachweis der Membrangängigkeit von Calpain-Inhibitoren benutzen wir humane Plättchen.

Calpain-vermittelter Abbau der Tyrosinkinase pp60src in Plättchen

Nach der Aktivierung von Plättchen wird die Tyrosinkinase pp60src durch Calpain gespalten. Dies wurde von Oda et al. in J. Biol. Chem., 1993, Vol 268, 12603-12608 eingehend untersucht. Hierbei wurde gezeigt, daß die Spaltung von pp60src durch Calpeptin, einen Inhibitor für Calpain, verhindert werden kann. In Anlehnung an diese Publikation wurde die zellulare Effektivität unserer Substanzen getestet. Frisches humanes, mit Zitrat versetztes Blut wurde 15 min. bei 200g zentrifugiert. Das Plättchen-reiche Plasma wurde gepoolt und mit Plättchenpuffer 1:1 verdünnt (Plättchenpuffer: 68 mM NaCl, 2,7 mM KCl, 0,5 mM $MgCl_2$ x 6 H_2O, 0,24 mM NaH_2PO_4 x H_2O, 12 mM $NaHCO_3$, 5,6 mM Glukose, 1 mM EDTA, pH 7,4). Nach einem Zentrifugations-und Waschschritt mit Plättchenpuffer wurden die Plättchen auf 10^7Zellen/ml eingestellt. Die Isolierung der humanen Plättchen erfolgte bei RT.

Im Testansatz wurden isolierte Plättchen (2 x 10^6) mit unterschiedlichen Konzentrationen an Inhibitoren (gelöst in DMSO) für 5 min. bei 37°C vorinkubiert. Anschließend erfolgte die Aktivierung der Plättchen mit 1µM Ionophor A23187 und 5 mM $CaCl_2$. Nach 5 min. Inkubation wurden die Plättchen kurz bei 13000 rpm zentrifugiert und das Pellet in SDS-Probenpuffer aufgenommen (SDS-Probenpuffer: 20 mM Tris-HCl, 5 mM EDTA, 5 mM EGTA, 1 mM DTT, 0,5 mM PMSF, 5 µg/ml Leupeptin, 10 µg/ml Pepstatin, 10% Glycerin und 1% SDS). Die Proteine wurden in einem 12%igen Gel aufgetrennt und pp60src und dessen 52-kDa und 47-kDa Spaltprodukte durch Western-Blotting identifiziert. Der verwendete polyklonale Kaninchen-Antikörper Anti-Cys-src ($pp60^{c-src}$) wurde von der Firma Biomol Feinchemikalien (Hamburg) erworben. Dieser primäre Antikörper wurde mit einem HRP-gekoppelten zweiten Antikörper aus der Ziege (Boehringer Mannheim, FRG) nachgewiesen. Die Durchführung des Western-Blotting erfolgte nach bekannten Methoden.

Die Quantifizierung der Spaltung von pp60src erfolgte densitometrisch, wobei als Kontrollen nicht-aktivierte (Kontrolle 1: keine Spaltung) und mit Ionophor- und Kalzium-behandelte Plättchen (Kontrolle 2: entspricht 100% Spaltung) verwendet wurden. Der ED_{50} -Wert entspricht der Konzentration an Inhibitor bei der die Intensität der Farbreaktion um 50% reduziert wird.

Glutamat induzierter Zelltod an corticalen Neuronen

Der Test wurde, wie bei Choi D. W., Maulucci-Gedde M. A. and Kriegstein A. R., "Glutamate neurotoxicity in cortical cell culture". *J. Neurosci.* 1989,7, 357-368, durchgeführt.

Aus 15 Tage alten Mäuseembryos wurden die Cortexhälften präpariert und die Einzelzellen enzymatisch (Trypsin) gewonnen. Diese Zellen (Glia und corticale Neuronen) werden in 24 Well-Platten ausgesät. Nach drei Tagen (Laminin beschichteten Platten) oder sieben Tagen (Ornithin beschichteten Platten) wird mit FDU (5-Fluor-2-Desoxyuridine) die Mitosebehandlung durchgeführt. 15 Tage nach der Zellpräparation wird durch Zugabe von Glutamat (15 Minuten) der Zelltod ausgelöst. Nach der Glutamatentfernung werden die Calpaininhibitoren zugegeben. 24 Stunden später wird durch die Bestimmung der Lactatdehydrogenase (LDH) im Zellkulturüberstand die Zellschädigung ermittelt.

Man postuliert, daß Calpain auch eine Rolle im apoptotischen Zelltod spielt (M.K.T.Squier et al. J.Cell.Physiol. 1994, 159, 229-237; T.Patel et al. Faseb Journal 1996, 590, 587-597). Deshalb wurde in einem weiteren Modell in einer humanen Zellinie der Zelltod mit Kalzium in Gegenwart eines Kalziumionophors ausgelöst. Calpain-Inhibitoren müssen in die Zelle gelangen und dort Calpain hemmen, um den ausgelösten Zelltod zu verhindern.

Kalzium-vermittelter Zelltod in NT2 Zellen

In der humanen Zellinie NT2 läßt sich durch Kalzium in Gegenwart des Ionophors A 23187 der Zelltod auslösen. 10^5 Zellen/well wurden in Mikrotiterplatten 20 Stunden vor dem Versuch ausplattiert. Nach diesem Zeitraum wurden die Zellen mit verschiedenen Konzentrationen an Inhibitoren in Gegenwart von 2,5 µM Ionophor und 5 mM Kalzium inkubiert. Dem Reaktionsansatz wurden nach 5 Stunden 0,05 ml XTT (Cell Proliferation Kit II, Boehringer Mannnheim) hinzugegeben. Die optische Dichte wird ungefähr 17 Stunden später, entsprechend den Angaben des Herstellers, in dem Easy Reader EAR 400 der Firma SLT bestimmt. Die optische Dichte, bei der die Hälfte der Zellen abgestorben sind, errechnet sich aus den beiden Kontrollen mit Zellen ohne Inhibitoren, die in Abwesenheit und Gegenwart von Ionophor inkubiert wurden.

Bei einer Reihe von neurologischen Krankheiten oder psychischen Störungen treten erhöhte Glutamat-Aktivitäten auf, die zu Zuständen von Übererregungen oder toxischen Effekten im zentralen Nervensystem (ZNS) führen. Glutamat vermittelt seine Effekte über verschiedene Rezeptoren. Zwei von diesen Rezeptoren werden nach den spezifischen Agonisten NMDA-Rezeptor und AMPA-Rezeptor klassifiziert. Antagonisten gegen diese Glutamat vermittelten Effekte

können somit zur Behandlung dieser Krankheiten eingesetzt werden, insbesondere zur therepeutischen Anwendung gegen neurodegenerativen Krankheiten wie Chorea Huntington und Parkinsonsche Krankheit, neurotoxischen Störungen nach Hypoxie, Anoxie, Ischämie und nach Lesionen, wie sie nach Schlaganfall und Trauma auftreten, oder auch als Antiepileptika (vgl. Arzneim.Forschung 1990, 40, 511-514; TIPS, 1990, 11, 334-338; Drugs of the Future 1989, 14, 1059-1071). De

Schutz gegen zerebrale Übererregung durch exzitatorische Aminosäuren (NMDA- bzw. AMPA-Antagonismus an der Maus)

Durch intrazerebrale Applikation von exzitatorischen Aminosäuren EAA (Excitatory Amino Acids) wird eine so massive Übererregung induziert, daß diese in kurzer Zeit zu Krämpfen und zum Tod der Tiere(Maus) führt. Durch systemische, z.B. intraperitoneale, Gabe von zentral-wirksamen Wirkstoffen (EAA-Antagonisten) lassen sich diese Symptome hemmen. Da die excessive Aktivierung von EAA-Rezeptoren des Zentralnervensystems in der Pathogenese verschiedener neurologischer Erkrankungen eine bedeutende Rolle spielt, kann aus dem nachgewiesenen EAA-Antagonismus in vivo auf eine mögliche therapeutische Verwendbarkeit der Substanzen gegen derartige ZNS-Erkrankungen geschlossen werden. Als Maß für die Wirksamkeit der Substanzen wurde ein ED_{50}-Wert bestimmt, bei dem 50% der Tiere durch eine festgelegte Dosis von entweder NMDA oder AMPA durch die vorangegangene ip.-Gabe der Meßsubstanz symptomfrei werden.

Die heterozyklisch substituierten Amide I stellen Inhibitoren von Cystein-Derivate wie Calpain I bzw. II und Cathepsin B bzw. L dar und können somit zur Bekämpfung von Krankheiten, die mit einer erhöhten Enzymaktivität der Calpain-Enzyme oder Cathepsin-Enzyme verbunden sind, dienen. Die vorliegenden Amide I können danach zur Behandlung von neurodegenerativen Krankheiten, die nach Ischämie, Trauma, Subarachnoidal-Blutungen und Stroke auftreten, und von neurodegenerativen Krankheiten wie multipler Infarkt-Dementia, Alzheimer Krankheit, Huntington Krankheit und von Epilepsien und weiterhin zur Behandlung von Schädigungen des Herzens nach cardialen Ischämien, Schädigungen der Nieren nach renalen Ischämien, Skelettmuskelschädigungen, Muskeldystrophien, Schädigungen, die durch Proliferation der glatten Muskelzellen entstehen, coronaren Vasospasmen, cerebralen Vasospasmen, Katarakten der Augen, Restenosis der Blutbahnen nach Angioplastie dienen. Zudem können die Amide I bei der Chemotherapie von Tumoren und deren Metastasierung nützlich sein und zur Behandlung von Krankheiten, bei denen ein erhöhter Interleukin-1-Spiegel auf-

tritt, wie bei Entzündungen und rheumatischen Erkrankungen, dienen.

Die erfindungsgemäßen Arzneimittelzubereitungen enthalten neben den üblichen Arneimittelhilfstoffen eine therapeutisch wirksame Menge der Verbindungen I.

Für die lokale äußere Anwendung, zum Beispiel in Puder, Salben oder Sprays, können die Wirkstoffe in den üblichen Konzentrationen enthalten sein. In der Regel sind die Wirkstoffe in einer Menge von 0,001 bis 1 Gew.-%, vorzugsweise 0,001 bis 0,1 Gew.-% enthalten.

Bei der inneren Anwendung werden die Präparationen in Einzeldosen verabreicht. In einer Einzeldosis werden pro kg Körpergewicht 0,1 bis 100 mg gegeben. Die Zubereitung können täglich in einer oder mehreren Dosierungen je nach Art und Schwere der Erkrankungen verabreicht werden.

Entsprechend der gewünschten Applikationsart enthalten die erfindungsgemäßen Arzneimittelzubereitungen neben dem Wirkstoff die üblichen Trägerstoffe und Verdünnungsmittel. Für die lokale äußere Anwendung können pharmazeutisch-technische Hilfsstoffe, wie Ethanol, Isopropanol, oxethyliertes Ricinusöl, oxethyliertes Hydriertes Ricinusöl, Polyacrylsäure, Polyethylenglykol, Polyethylenglykostearat, ethoxylierte Fettalkohole, Paraffinöl, Vaseline und Wollfett, verwendet werden. Für die innere Anwendung eignen sich zum Beispiel Milchzucker, Propylenglykol, Ethanol, Stärke, Talk und Polyvinylpyrrolidon.

Ferner können Antioxidationsmittel wie Tocopherol und butyliertes Hydroxyanisol sowie butyliertes Hydroxytoluol, geschmacksverbessernde Zusatzstoffe, Stabilisierungs-, Emulgier- und Gleitmittel enthalten sein.

Die neben dem Wirkstoff in der Zubereitung enthaltenen Stoffe sowie die bei der Herstellung der pharmazeutischen Zubereitungen verwendeten Stoffe sind toxikologisch unbedenklich und mit dem jeweiligen Wirkstoff verträglich. Die Herstellung der Arzneimittelzubereitungen erfolgt in üblicher Weise, zum Beispiel durch Vermischung des Wirkstoffes mit anderen üblichen Trägerstoffen und Verdünnungsmitteln.

Die Arzneimittelzubereitungen können in verschiedenen Applikationsweisen verabreicht werden, zum Beispiel peroral, parenteral wie intravenös durch Infusion, subkutan, intraperitoneal und topisch. So sind Zubereitungsformen wie Tabletten, Emulsionen,

Infusions- und Injektionslösungen, Pasten, Salben, Gele, Cremes, Lotionen, Puder und Sprays möglich.

Beispiele

Beispiel 1

2-((4-Phenylpiperazin-1-yl)methyl)benzoesäure-N-(3-phenyl-propan-1-al-2-yl)amid

a) 2-(4-Phenylpiperazin-1-ylmethyl)benzoesäuremethylester

10.0 g 2-Chlormethylbenzoesäuremethylester, 15 g Kalium-carbonat, 8.8 g Phenylpiperazin und eine Spatelspitze 18-Krone-6 wurden in 200 ml DMF 5 h bei 100 °C erhitzt und anschließend 60 h bei Raumtemperatur gerührt. Das überschüssige Kaliumcarbonat wurde abfiltriert, das Filtrat wurde eingeengt und der Rückstand zwischen Wasser und Essigester verteilt. Nach Trocknen der organischen Phase über Magnesiumsulfat und Einengen des Lösungsmittels fielen 16.8 g (100 %) des Produkts an.

b) 2-(4-Phenylpiperazin-1-ylmethyl)benzoesäure

16.8 g der Zwischenverbindung 1a wurden in 150 ml THF vorgelegt und mit 1.7 g LiOH in 150 ml Wasser bei Raumtemperatur versetzt. Die trübe Lösung wurde durch Zugabe von 10 ml MeOH geklärt. Die Reaktionsmischung wurde 12 h bei Raumtemperatur gerührt und mit einer äquimolaren Menge 1 M HCl hydrolysiert. Die Reaktionsmischung wurde bis zur Trockne eingeengt und der Rückstand in Methanol/Toluol aufgenommen. Nach Entfernen des Lösungsmittels fielen 15.2 g (86 %) des noch salzhaltigen Produkts an.

c) 2-((4-Phenylpiperazin-1-yl)methyl)benzoesäure-N-(3-phenyl-propan-1-ol-2-yl)amid

3.0 g der Zwischenverbindung 1b und 3 ml Triethylamin wurden in 50 ml DMF vorgelegt. Es wurden 5 g Natriumsulfat zugegeben und 30 min gerührt. 1.5 g Phenylalaninol, 1.4 g HOBT und 2.1 g EDC wurden nacheinander bei 0 °C zugegeben und über Nacht bei Raumtemperatur nachgerührt. Die Reaktionsmischung wurde auf destilliertes Wasser geschüttet, mit $NaHCO_3$ alkalisch gestellt, mit NaCl gesättigt und dreimal mit 100 ml Methylen-chlorid extrahiert. Die organischen Phasen wurden zweimal mit Wasser gewaschen und über Magnesiumsulfat getrocknet. Nach

Einengen des Lösungsmittels fielen 2.5 g (59 %) des Produkt an.

d) 2-((4-Phenylpiperazin-1-yl)methyl)benzoesäure-N-(3-phenyl-propan-1-al-2-yl)amid

2.3 g der Zwischenverbindung 1c wurden in Gegenwart von 2.4 g Triethylamin in 50 ml DMSO vorgelegt und mit 2.5 g SO_3-Pyridin-Komplex versetzt. Es wurde über Nacht bei Raumtemperatur gerührt. Der Ansatz wurde auf 250 ml destilliertes Wasser geschüttet, mit $NaHCO_3$ alkalisch gestellt, mit NaCl gesättigt, mit 100 ml Methylenchlorid extrahiert und über Magnesiumsulfat getrocknet. Nach dem Einengen des Lösungsmittels wurde der Rückstand in THF gelöst und mit HCl in Dioxan das Hydrochlorid ausgefällt. Der Niederschlag wurde abgesaugt und mehrfach mit Ether gewaschen, wobei 1.9 g (71 %) des Produkts anfielen.

1H-NMR (d_6-DMSO): δ = 2.9 (2H), 3.0-3.3 (8H), 4.1-4.5 (2H), 4.7 (1H), 6.8-7.7 (14H), 9.3 (1H), 9.8 (1H) ppm.

Beispiel 2

2-((4-Benzylpiperazin -1-yl)methyl)benzoesäure-N-(3-phenyl-propan-1-al-2-yl)amid

a) 2-((4-Benzylpiperazin-1-yl)methyl)benzoesäuremethylester

10.0 g 2-Chlormethylbenzoesäuremethylester und 9.6 g N-Benzylpiperazin wurden analog Beispiel 1a in 200 ml DMF in Gegenwart von 15 g Kaliumcarbonat bei 100 °C umgesetzt, wobei 17.6 g (100 %) des Produkts anfielen.

b) 2-((4-Benzylpiperazin-1-yl)methyl)benzoesäure

17.5 g der Zwischenverbindung 2a in 150 ml THF wurden analog Beispiel 1b mit 1.6 g LiOH in 150 ml Wasser hydrolysiert, wobei 9.1 g (54 %) des Produkts anfielen.

c) 2-((4-Benzylpiperazin-1-yl)methyl)benzoesäure-N-(3-phenyl-propan-1-ol-2-yl)amid

3.0 g der Zwischenverbindung 2b wurden analog Beispiel 1c in 60 ml DMF mit 3 ml Triethylamin, 1.5 g Phenylalaninol, 1.3 g HOBT und 2.0 g EDC versetzt, wobei 2.0 g (46 %) des Produkts anfielen.

d) 2-((4-Benzylpiperazin-1-yl)methyl)benzoesäure-N-(3-phenyl-propan-1-al-2-yl)amid

1.5 g der Zwischenverbindung 2c wurden analog Beispiel 1d in 40 ml DMSO in Gegenwart von 2.3 ml Triethylamin mit 1.9 g SO_3-Pyridin-Komplex in 20 ml DMSO oxidiert, wobei 0.4 g (21 %) des Produkts in Form des Fumarats anfielen.

1H-NMR (d_6-DMSO): δ = 2.1-2.3 (8H), 2.9-3.0 (1H), 3.3-3.6 (6H), 4.5 (1H), 6.6 (2H), 7.1-7.7 (14H), 9.7 (1H), 10.3 (1H) ppm.

Beispiel 3

2-((4-Benzylpiperazin-1-yl)methyl)benzoesäure-N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amid

a) 2-((4-Benzylpiperazin-1-yl)methyl)benzoesäure-N-(1-carbamoyl-1-ol-3-phenylpropan-2-yl)amid

1.5 g der Zwischenverbindung 1b wurden analog Beispiel 1c in 40 ml DMF mit 0.7 ml Triethylamin, 1.0 g 3-Amino-2-hydroxy-4-phenylbuttersäureamid-Hydrochlorid, 0.6 g HOBT und 0.9 g EDC versetzt, wobei 0.8 g (38 %) des Produkts anfielen.

b) 2-((4-Benzylpiperazin-1-yl)methyl)benzoesäure-N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amid

0.7 g der Zwischenverbindung 3a wurden analog Beispiel 1d in 20 ml DMSO in Gegenwart von 0.8 g Triethylamin mit 0.7 g SO_3-Pyridin-Komplex oxidiert, wobei 0.1 g (18 %) des Produkts in Form der freien Base anfielen.

1H-NMR (d_6-DMSO): δ = 2.3 (4H), 2.8-3.5 (8H), 5.3 (1H), 6.7-7.5 (16H), 7.8 (1H), 8.1 (1H), 10.3 (1H) ppm.

Beispiel 4

2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)benzoesäure-N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amid

a) 2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)benzoesäure-methylester

4.0 g 2-Chlormethylbenzoesäremethylester und 4.4 g 3-Methylphenylpiperazin wurden in 200 ml DMF in Gegenwart von 4.5 g Kaliumcarbonat 3 h bei 140 °C erhitzt. Die Reaktionsmischung wurde auf Wasser geschüttet und dreimal mit Essigester extrahiert. Die vereinigten organischen Phasen wurden dreimal mit gesättigter Kochsalzlösung gewaschen, über Magnesiumsulfat getrocknet und eingeengt, wobei 6.5 g (92 %) des Produkts anfielen.

b) 2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)benzoesäure

5.9 g des Zwischenprodukts 4a wurde in 75 ml THF gelöst und analog Beispiel 1b mit 0.9 g LiOH in 75 ml Wasser hydrolysiert, wobei 2.9 g (51 %) des Produkts anfielen.

c) 2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)benzoesäure-N-(1-carbamoyl-1-ol-3-phenylpropan-2-yl)amid

1.8 g der Zwischenverbindung 4b wurden analog Beispiel 1c in 50 ml DMF in Gegenwart von 2.7 ml Triethylamin vorgelegt und nacheinander mit 0.8 g HOBT, 1.3 g 3-Amino-2-hydroxy-4-phenylbuttersäureamid-Hydrochlorid und 1.2 EDC versetzt, wobei 1.4 g (50 %) des Produkts anfielen.

d) 2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)benzoesäure-N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amid

1.2 g der Zwischenverbindung 4c wurden analog Beispiel 1d in 30 ml DMSO gelöst und in Gegenwart von 1.5 ml Triethylamin mit 1.6 g SO_3-Pyridin-Komplex oxidiert, wobei 1.0 g (83 %) des Produkts anfielen.

MS: m/e = 484 (M^+)

Beispiele 5 und 6 wurden analog Beispiel 1 synthetisiert.

Beispiel 5

3-((4-Phenylpiperazin-1-yl)methyl)benzoesäure-N-(3-phenylpropan-1-al-2-yl)amid -Fumarat

1H-NMR (d_6-DMSO): δ = 2.5 (4H), 2.9 (1H), 3.2 (4H), 3.3 (1H), 3.7 (2H), 4.5 (1H), 6.6 (2H), 6.75 (1H), 6.9 (2H), 7.2 (2H), 7.2-7.3 (5H), 7.45 (1H), 7.55 (1H), 7.75 (1H), 7.8 (2H), 8.9 (1H), 9.7 (1H) ppm.

Beispiel 6

3-((4-(2-*tert*-Butyl-4-trifluormethylpyrimidin-6-yl)homopiperazin-1-yl)methyl)benzoesäure-N-(3-phenylpropan-1-al-2-yl)amid

MS: m/e = 568 (M^++1)

Beispiel 7

4-(N-(3,4-Dioxomethylen)benzyl-N-methylaminomethyl)benzoesäure-N-(3-phenylpropan-1-al-2-yl)amid

a) 4-(N-(3,4-Dioxomethylen)benzyl-N-methylaminomethyl)benzoesäure

11.5 g N-(3,4-Dioxomethylen)benzyl-N-methylamin und 15.5 g Triethylamin wurden in vorgelegt und mit 15.0 g 4-Brommethylbenzoesäure in 100 ml THF versetzt. Die Reaktionsmischung wurde kurz zum Rückfluß erhitzt und anschließend 15 h bei Raumtemperatur nachgerührt. Nach Abfiltrieren der Salze wurde die Mutterlauge eingeengt, der Rückstand in Essigester gelöst und mit Wasser gewaschen. Die wäßrige Phase wurde alkalisch gestellt und mit Essigester mehrfach extrahiert, wobei 6.6 g (32 %) des Produkts als weißer Feststoff anfielen.

b) 4-(N-(3,4-Dioxomethylen)benzyl-N-methylaminomethyl)benzoesäure-N-(3-phenylpropan-1-ol-2-yl)amid

4.4 g der Zwischenverbindung 5a wurden analog Beispiel 1c in 50 ml DMF in Gegenwart von 2.9 ml Triethylamin vorgelegt und nacheinander mit 1.8 g HOBT, 2.0 g Phenylalanin und 2.8 EDC versetzt, wobei 2.3 g (40 %) des Produkts anfielen.

c) 4-(N-(3,4-Dioxomethylen)benzyl-N-methylaminomethyl)benzoesäure-N-(3-phenylpropan-1-al-2-yl)amid

2.0 g der Zwischenverbindung 5b wurden analog Beispiel 1d in 60 ml DMSO gelöst und in Gegenwart von 1.8 ml Triethylamin mit 2.1 g SO_3-Pyridin-Komplex oxidiert, wobei 1.3 g (68 %) des Produkts anfielen.

1H-NMR (CF_3COOD): δ = 2.9 (3H), 3.2 (2H), 4.3-4.9 (5H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.2-7.4 (5H), 7.8 (2H), 8.25 (2H) ppm.

MS: m/e = 430 (M^+)

Beispiele 8-28 wurden analog Beispiel 7 dargestellt.

Beispiel 8

4-(N-Benzyl-N-methylaminomethyl)benzoesäure-N-(3-phenylpropan-1-al-2-yl)amid

1H-NMR (CF_3COOD): δ = 2.9 (3H), 3.2 (2H), 4.3-5.0 (5H), 6.7 (1H), 7.25-7.5 (8H), 7.55 (2H), 7.8 (2H), 8.2 (2H) ppm.

MS: m/e = 386 (M^+)

Beispiel 9

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoesäure-N-(3-phenylpropan-1-al-2-yl)amid

1H-NMR (CF_3COOD): δ = 2.9 (3H), 3.3 (2H), 4.0 (3H), 4.3-4.9 (5H), 6.7 (1H), 7.1-7.4 (7H), 7.5 (2H), 7.8 (2H), 8.2 (2H) ppm.

MS: m/e = 416 (M^+)

Beispiel 10

4-(N-Benzyl-N-methylaminomethyl)benzoesäure-N-(3-butan-1-al-2-yl)amid

1H-NMR (CF_3COOD): δ = 1.1 (3H), 1.6 (2H), 2.0 (2H), 2.9 (3H), 4.3-4.5 (3H), 4.7 (1H), 4.8 (1H), 6.6 (1H), 7.3-7.6 (5H), 7.8 (2H), 8.3 (2H) ppm.

MS: m/e = 338 (M^+)

Beispiel 11

4-(N-(3,4-Dioxomethylen)benzyl-N-methylaminomethyl)benzoesäure-N-(3-butan-1-al-2-yl)amid

1H-NMR (CF_3COOD): δ = 1.1 (3H), 1.6 (2H), 1.9 (2H), 2.9 (3H), 4.25-4.6 (4H), 4.75 (1H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.8 (2H), 8.3 (2H) ppm.

MS: m/e = 382 (M^+)

Beispiel 12

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoesäure-N-(3-butan-1-al-2-yl)amid

MS: m/e = 368 (M^+)

Beispiel 13

4-(N-(3,4-Dioxomethylen)benzyl-N-methylaminomethyl)benzoesäure-N-(3-cyclohexylpropan-1-al-2-yl)amid

1H-NMR (CF_3COOD): δ = 1.0-2.0 (13H), 2.9 (3H), 4.3-4.9 (4H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.8 (2H), 8.3 (2H) ppm.

MS: m/e = 436 (M^+)

Beispiel 14

4-(N-(4-Benzyl-N-methylaminomethyl)benzoesäure-N-(3-cyclohexylpropan-1-al-2-yl)amid

1H-NMR (d_6-DMSO): δ = 1.0-1.8 (13H), 2.1 (3H), 3.4 (2H), 3.5 (2H), 4.3 (1H), 7.1-7.4 (5H), 7.5 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

Beispiel 15

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoesäure-N-(3-cyclohexylpropan-1-al-2-yl)amid

1H-NMR ($CDCl_3$): δ = 1.0-1.8 (13H), 2.1 (3H), 3.4 (2H), 3.5 (2H), 3.7 (3H), 4.3 (1H), 6.8 (2H), 7.25 (2H), 7.5 (2H), 7.9 (2H), 8.8 (1H), 9.5 (1H) ppm.

Beispiel 16

4-((2-Phenylpyrrolid-1-yl)methyl)benzoesäure-N-(3-cyclohexylpropan-1-al-2-yl)amid

MS: m/e = 420 (M^+)

Beispiel 17

4-((2-Phenylpyrrolid-1-yl)methyl)benzoesäure-N-(3-butan-1-al-2-yl)amid

MS: m/e = 364 (M^+)

Beispiel 18

4-((2-Phenylpyrrolid-1-yl)methyl)benzoesäure-N-(3-phenylpropan-1-al-2-yl)amid

MS: m/e = 412 (M^+)

Beispiel 19

4-((1,2,3,4-Dihydrochinolin-1-yl)methyl)benzoesäure-N-(3-cyclohexylpropan-1-al-2-yl)amid

1H-NMR ($CDCl_3$): δ = 1.0-1.9 (13H), 2.0 (2H), 2.8 (2H), 3.3 (2H), 4.5 (2H), 4.8 (1H), 6.4 (1H), 6.5 (2H), 7.0 (2H), 7.4 (2H), 7.8 (2H), 9.7 (1H) ppm.

MS: m/e = 404 (M^+)

Beispiel 20

4-((1,2,3,4-Dihydrochinolin-1-yl)methyl)benzoesäure-N-(3-phenylpropan-1-al-2-yl)amid

1H-NMR (d_6-DMSO): δ = 1.9 (2H), 2.75 (2H), 2.9 (1H), 3.3 (1H), 3.4 (2H), 4.4 (1H), 4.5 (2H), 6.3 (2H), 6.8 (2H), 7.1-7.25 (5H), 7.3 (2H), 7.7 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 398 (M^+)

Beispiel 21

4-((1,2,3,4-Dihydrochinolin-1-yl)methyl)benzoesäure-N-(3-butan-1-al-2-yl)amid

1H-NMR (d_6-DMSO): δ = 0.9 (3H), 1.2-2.0 (6H), 2.7 (2H), 3.3 (2H), 4.2 (1H), 4.5 (2H), 6.4 (2H), 6.8 (2H), 7.3 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 350 (M^+)

Beispiel 22

4-((1,2,3,4-Dihydroisochinolin-2-yl)methyl)benzoesäure-N-(3-cyclohexylpropan-1-al-2-yl)amid

1H-NMR (d_6-DMSO): δ = 0.9-1.8 (13H), 2.7-2.9 (4H), 3.6 (2H), 3.75 (2H), 4.4 (1H), 6.9-7.1 (4H), 7.4 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 404 (M^+)

Beispiel 23

4-((1,2,3,4-Dihydroisochinolin-2-yl)methyl)benzoesäure-N-(3-phenylpropan-1-al-2-yl)amid

1H-NMR (d_6-DMSO): δ = 2.7 (2H), 2.8 (2H), 2.9 (1H), 3.2 (1H), 3.5 (2H), 3.7 (2H), 4.5 (1H), 6.9-7.1 (4H), 7.2-7.3 (5H), 7.5 (2H), 7.75 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 398 (M^+)

Beispiel 24

4-((1,2,3,4-Dihydroisochinolin-2-yl)methyl)benzoesäure-N-(3-butan-1-al-2-yl)amid-Hydrochlorid

1H-NMR (d_6-DMSO): δ = 0.9 (3H), 1.2-2.0 (4H), 3.0 (1H), 3.3 (2H), 3.6 (1H), 4.1-4.6 (5H), 7.2 (4H), 7.8 (2H), 8.0 (2H), 9.0 (1H), 9.5 (1H), 11.75 (1H) ppm.

Beispiel 25

4-((6,7-Dimethoxy-1,2,3,4-dihydroisochinolin-2-yl)methyl)benzoesäure-N-(3-cyclohexylpropan-1-al-2-yl)amid

1H-NMR (d_6-DMSO): δ = 0.9-1.9 (13H), 2.7 (4H), 3.4 (2H), 3.6 (3H), 3.65 (2H), 3.7 (3H), 4.3 (1H), 6.5 (1H), 6.6 (1H), 7.5 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 464 (M^+)

Beispiel 26

4-((6,7-Dimethoxy-1,2,3,4-dihydroisochinolin-2-yl)methyl)benzoesäure-N-(3-phenylpropan-1-al-2-yl)amid

1H-NMR (d_6-DMSO): δ = 2.7 (4H), 2.9 (1H), 3.25 (1H), 3.6 (6H), 3.7 (2H), 4.5 (1H), 6.6 (1H), 6.7 (1H), 7.2-7.3 (5H), 7.4 (2H), 7.8 (2H), 8.9 (1H), 9.6 (1H) ppm.

MS: m/e = 458 (M^+)

Beispiel 27

4-((6,7-Dimethoxy-1,2,3,4-dihydroisochinolin-2-yl)methyl)benzoesäure-N-(3-butan-1-al-2-yl)amid

1H-NMR (d_6-DMSO): δ = 0.9 (3H), 1.4 (2H), 1.5-1.8 (2H), 2.7 (4H), 3.4 (2H), 3.7 (3H), 3.75 (3H), 3.8 (2H), 4.3 (1H), 6.6 (1H), 6.7 (1H), 7.4 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

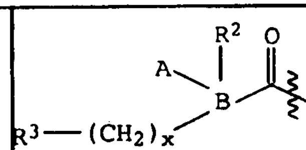
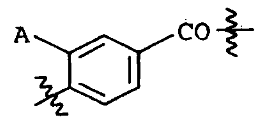
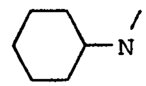
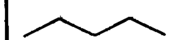
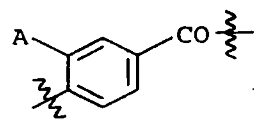
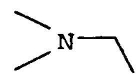
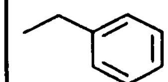
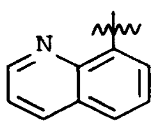
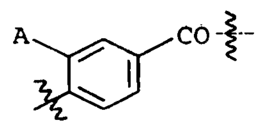
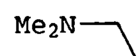
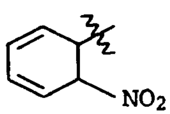
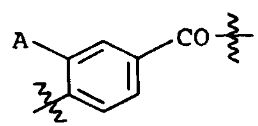
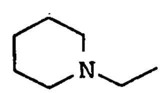
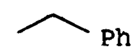
MS: m/e = 410 (M^+)

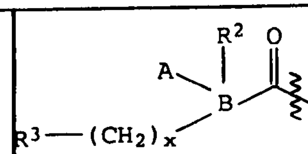
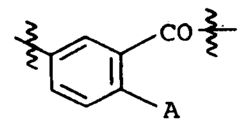
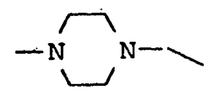
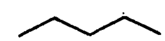
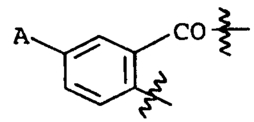
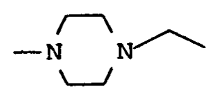
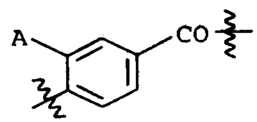
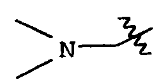
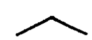
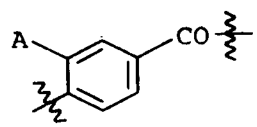
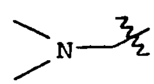
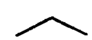
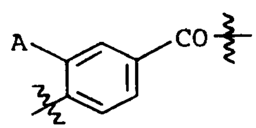
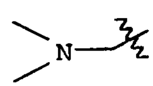
Beispiel 28

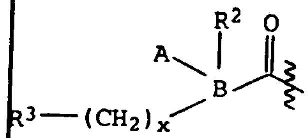
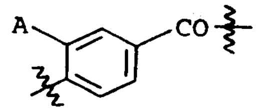
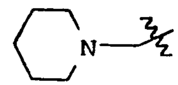
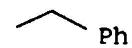
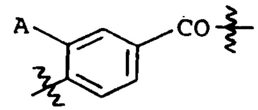
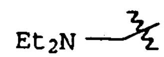
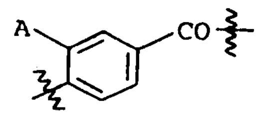
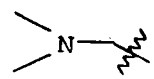
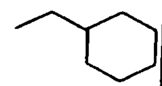
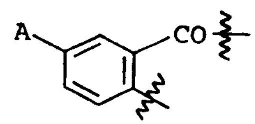
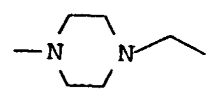
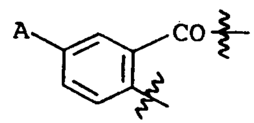
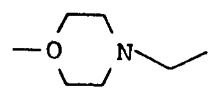
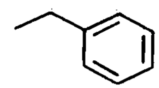
2-((1,2,3,4-Dihydrochinolin-1-yl)methyl)benzoesäure-N-(3-butan-1-al-2-yl)amid

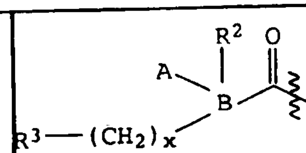
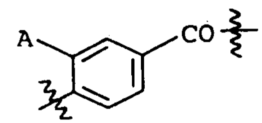
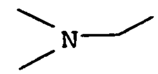
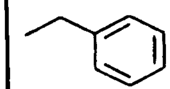
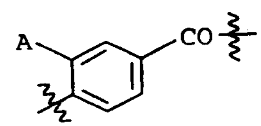
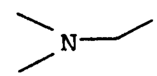
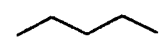
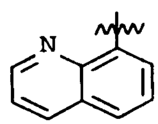
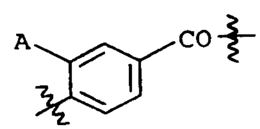
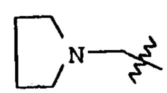
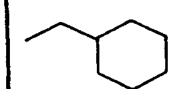
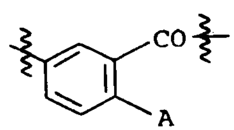
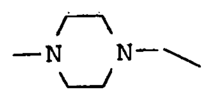
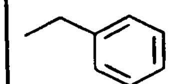
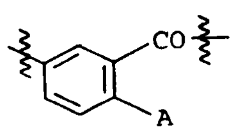
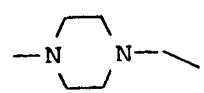
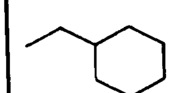
MS: m/e = 441 (M^+)

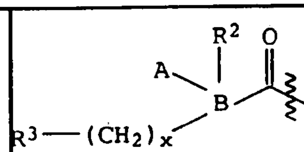
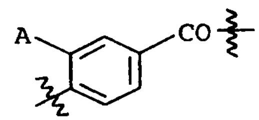
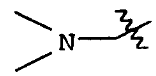
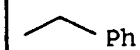
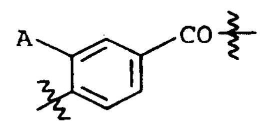
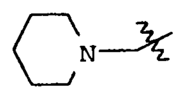
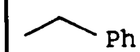
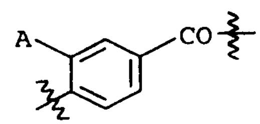
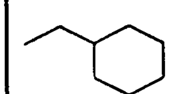
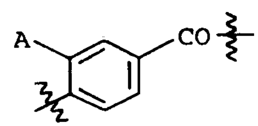
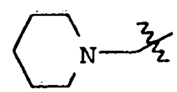
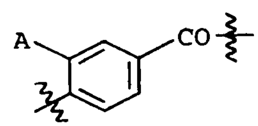
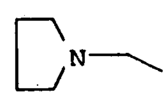
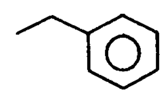
Tabelle

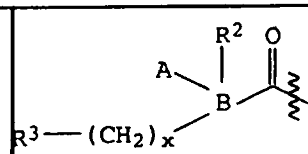
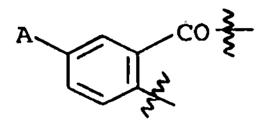
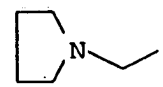
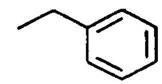
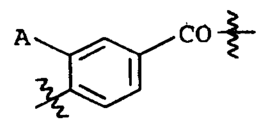
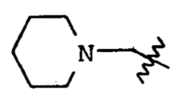
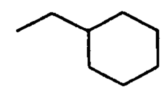
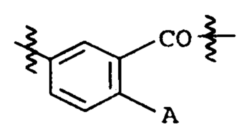
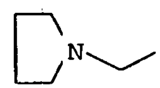
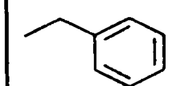
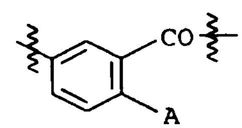
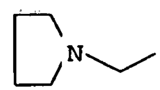
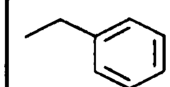
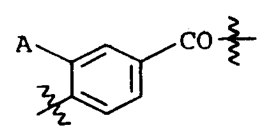
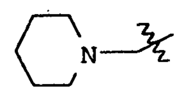
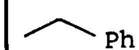
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
1	Bu	SO_2NH	H				H
2	2-Py	SO_2NH	H				H
3		SO_2NH	H				H
4		SO_2NH	H				H

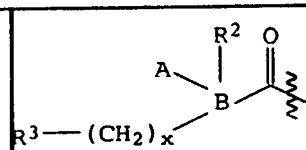
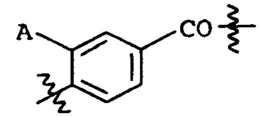
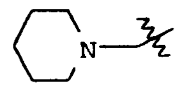
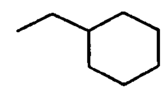
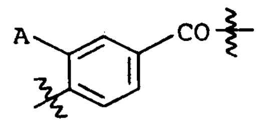
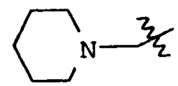
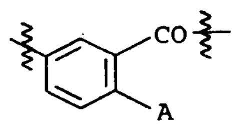
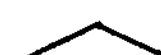
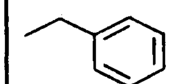
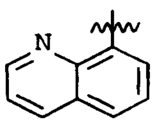
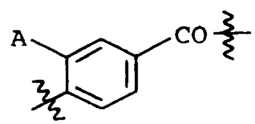
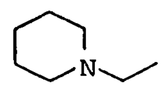
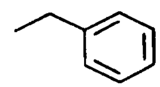
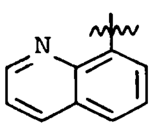
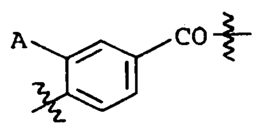
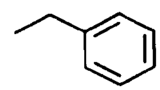
Nr.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
5	Ph	CH_2O	H				H
6	2-Py	CH_2O	H				H
7	Bu	SO_2NH	H			 Ph	H
8	Naphth	SO_2NH	H			 Ph	H
9	Naphth	SO_2NH	H			 Ph	$CONH_2$

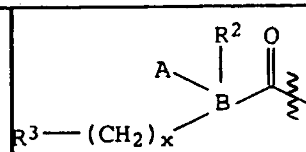
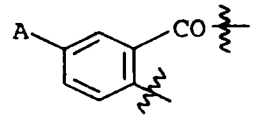
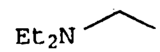
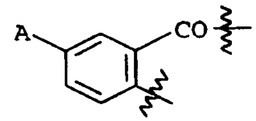
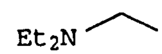
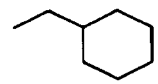
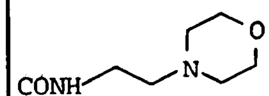
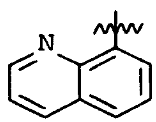
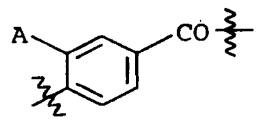
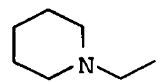
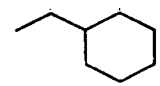
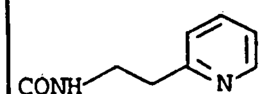
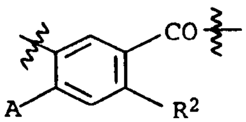
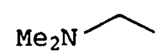
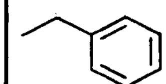
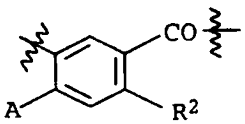
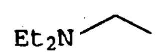
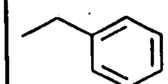
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
10	Ph	SO_2NH	H				H
11	Bu	SO_2NH	H				$CONH_2$
12	Naphth	SO_2NH	H				$CONH_2$
13	Ph	-O-	H				H
14	Ph	-S-	H				$CONH_2$

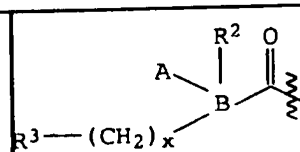
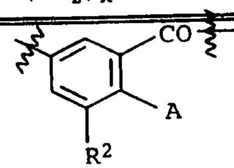
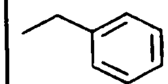
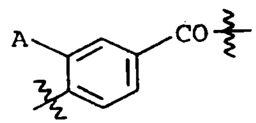
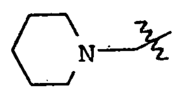
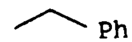
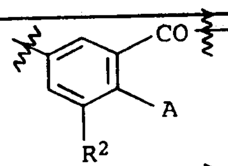
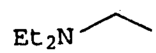
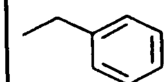
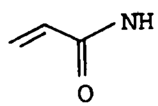
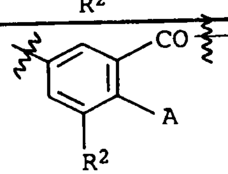
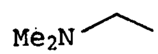
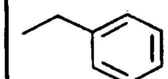
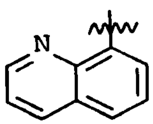
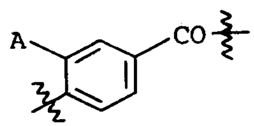
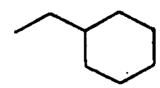
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
15	2-Py	SO_2NH	H				$CONH_2$
16	2-Py	SO_2NH	H				H
17		SO_2NH	H				H
18	Ph	-O-	H				H
19	Ph	-S-	H				$CONH_2$

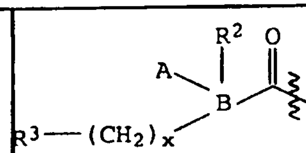
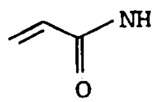
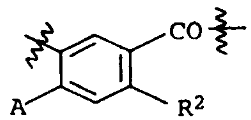
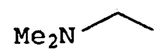
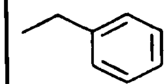
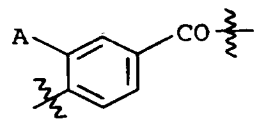
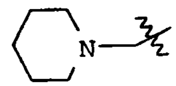
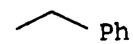
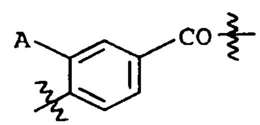
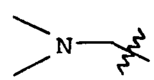
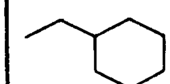
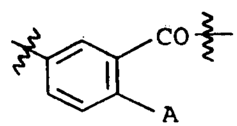
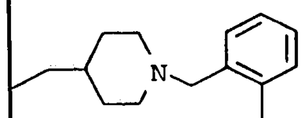
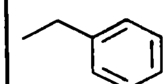
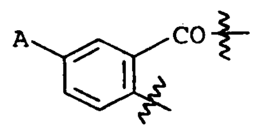
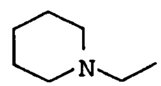
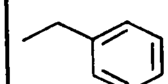
Nr.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
20	Bu	SO_2NH	H				$CONH_2$
21	Naphth	SO_2NH	H				H
22	Ph	SO_2NH	H		Et_2N		H
23	Bu	SO_2NH	H				$CONH_2$
24	2-Py	SO_2NH	H				H

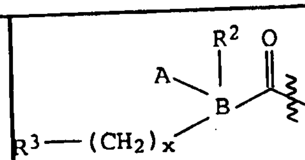
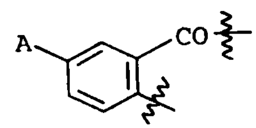
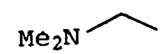
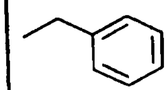
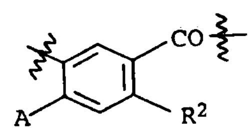
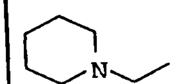
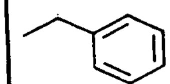
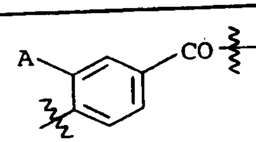
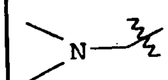
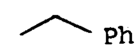
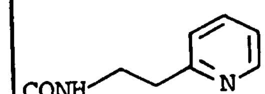
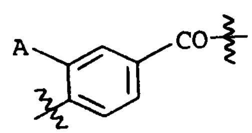
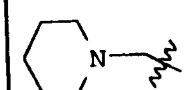
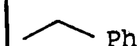
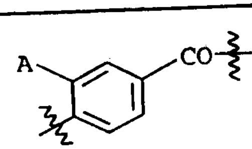
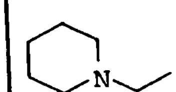
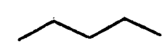
Nr.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
25	Ph	-O-	H				$CONH_2$
26	2-Py	SO_2NH	H				H
27	Ph	-O-	H				$CONH_2$
28	Ph	-O-	H				H
29	Naphth	SO_2NH	H				$CONH_2$

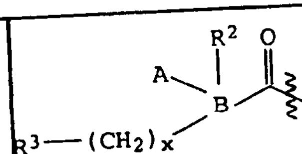
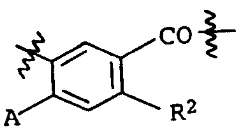
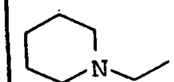
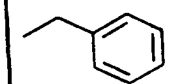
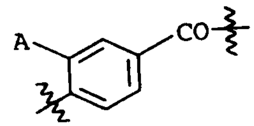
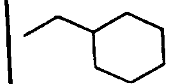
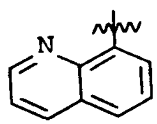
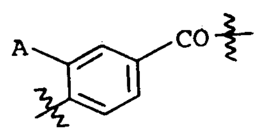
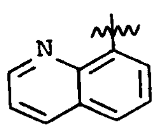
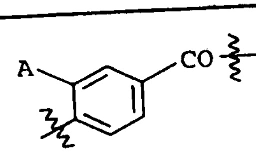
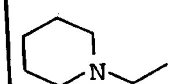
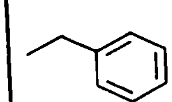
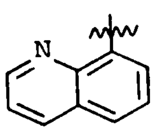
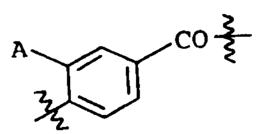
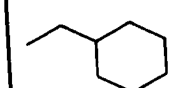
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
30	Bu	SO_2NH	H				H
31	2-Py	SO_2NH	H				$CONH_2$
32	Ph	-O-	H		Et_2N 		H
33		SO_2NH	H				$CONH_2$
34		SO_2NH	H				H

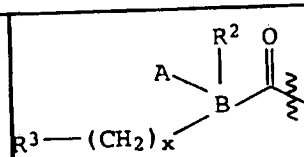
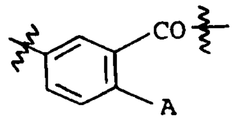
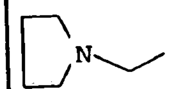
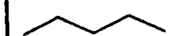
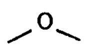
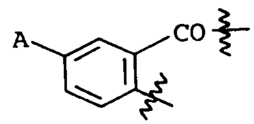
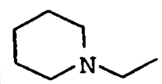
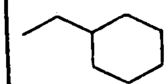
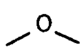
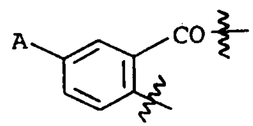
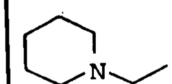
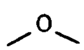
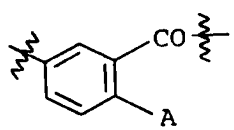
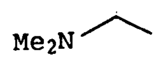
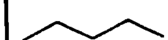
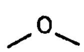
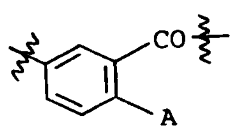
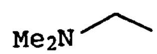
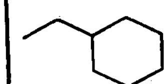
Nr.	R1	A	R2		R^3—$(CH_2)_x$—	R^4	R^5
35	Ph	-O-	H				$CONH_2$
36	Ph	-O-	H				
37		SO_2NH	H				
38	Ph	CONH	MeO				H
39	Naphth	CONH	MeO				H

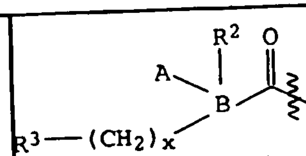
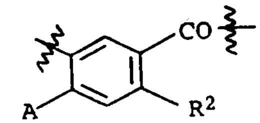
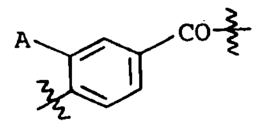
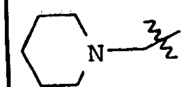
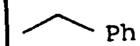
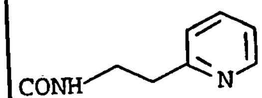
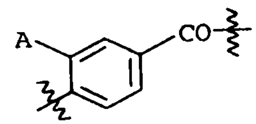
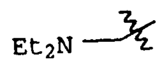
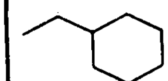
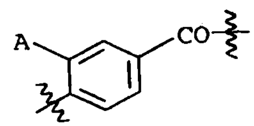
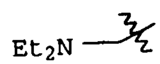
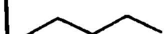
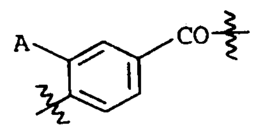
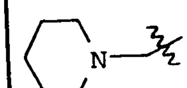
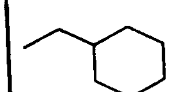
Nr.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
40	Ph	CONH	Et				H
41	Bu	SO_2NH	H				H
42	Naphth	CONH	Et				H
43	Ph		Et				H
44		SO_2NH	H				$CONH_2$

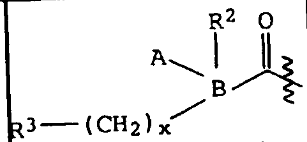
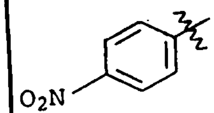
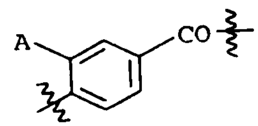
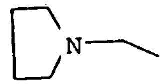
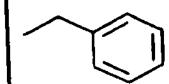
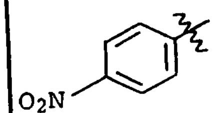
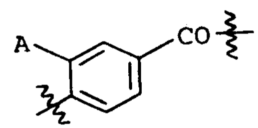
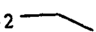
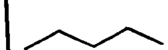
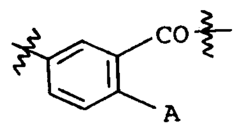
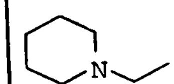
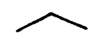
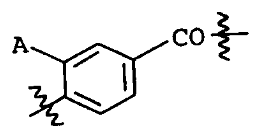
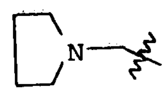
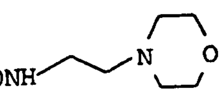
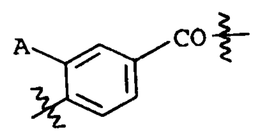
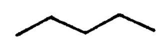
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
45	Ph		MeO				H
46	Bu	SO_2NH	H				$CONH_2$
47	Naphth	SO_2NH	H				H
48	H	m=o=O	H				H
49	Ph	-O-	H				H

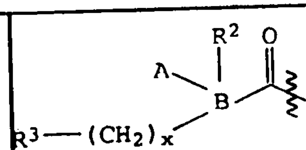
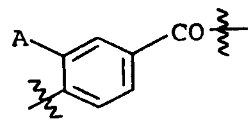
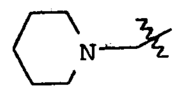
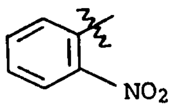
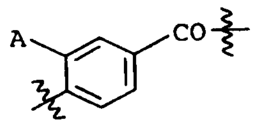
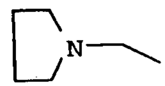
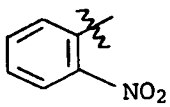
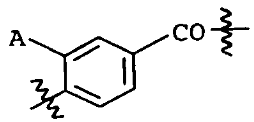
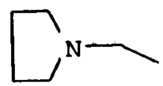
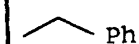
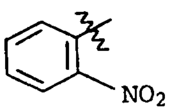
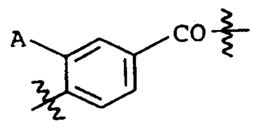
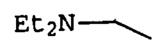
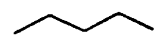
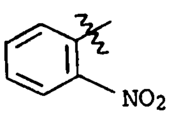
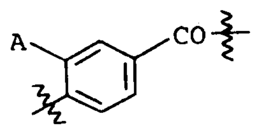
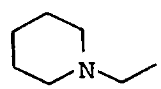
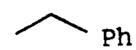
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
50	Ph	-O-	H				$CONH_2$
51	Naphth	CONH	MeO				$CONH_2$
52	Bu	SO_2NH	H				
53	Ph	SO_2NH	H				$CONH_2$
54	2-Py	SO_2NH	H				H

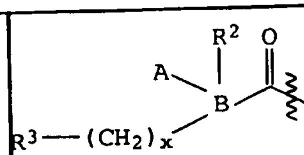
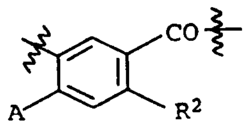
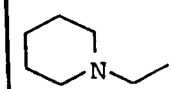
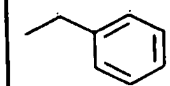
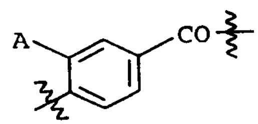
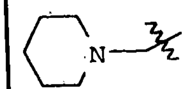
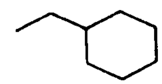
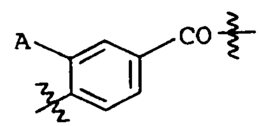
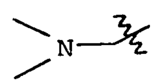
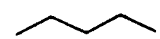
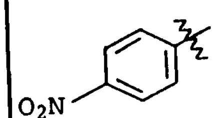
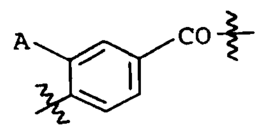
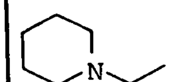
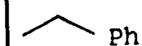
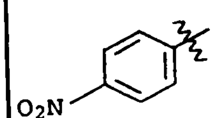
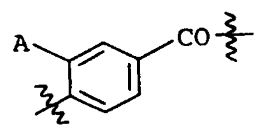
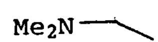
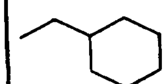
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
55	Ph	CONH	MeO				$CONH_2$
56	Bu	SO_2NH	H		Et_2N—		H
57		SO_2NH	H		Me_2N		$CONH_2$
58		SO_2NH	H				H
59		SO_2NH	H		Et_2N		H

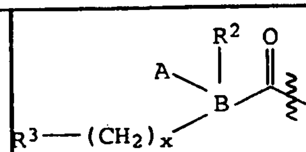
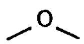
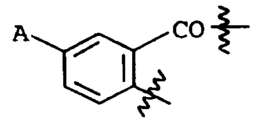
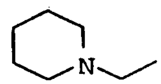
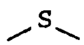
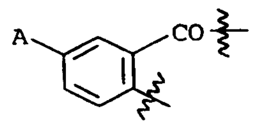
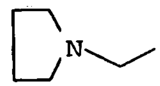
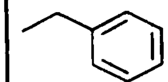
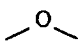
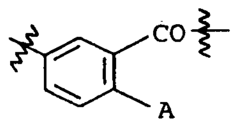
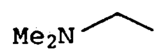
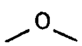
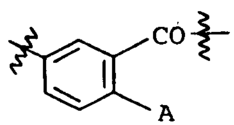
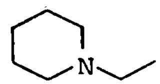
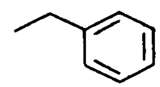
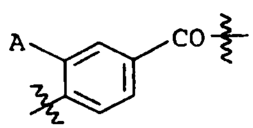
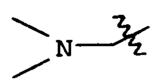
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
60	Ph	CONH	Et				$CONH_2$
61	Ph		H				H
62	Ph		H				H
63	Ph		H				$CONH_2$
64	Ph		H				$CONH_2$

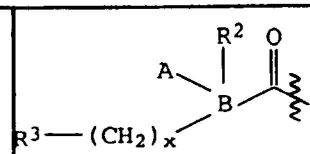
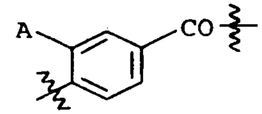
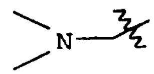
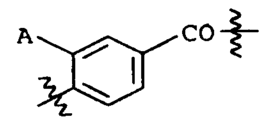
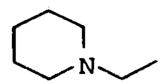
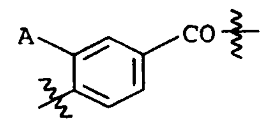
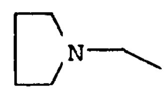
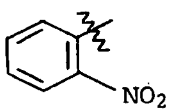
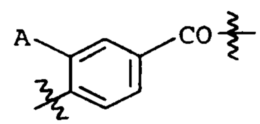
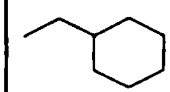
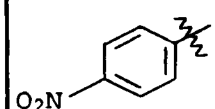
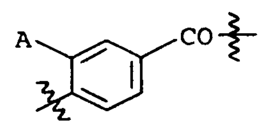
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
65	Ph	CONH	MeO				$CONH_2$
66	Ph	SO_2NH	H				
67	Ph	SO_2NH	H				$CONH_2$
68	Ph	SO_2NH	H				H
69	Bu	SO_2NH	H				$CONH_2$

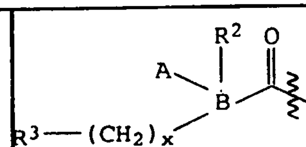
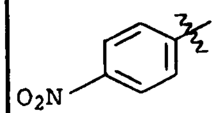
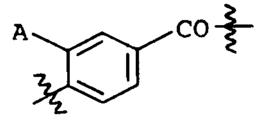
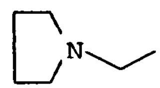
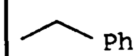
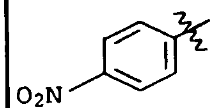
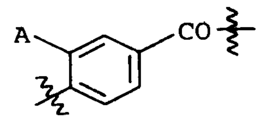
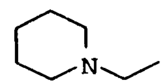
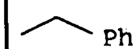
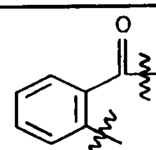
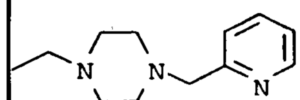
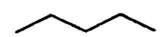
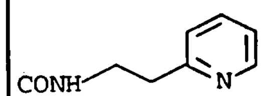
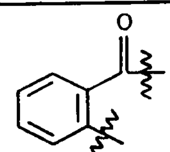
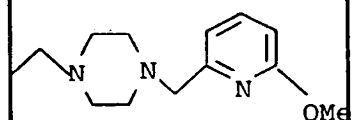
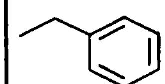
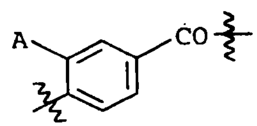
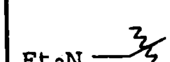
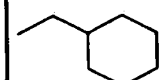
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
70		SO_2NH	H				H
71		SO_2NH	H		Et_2 		$CONH_2$
72	Ph	CONH	Et			 Ph	H
73	Bu	SO_2NH	H			 Ph	CONH 
74	Ph	SO_2NH	H		Et_2N 		$CONH_2$

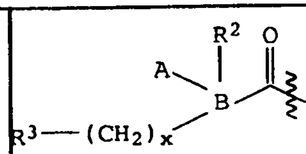
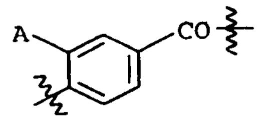
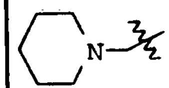
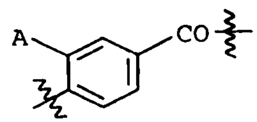
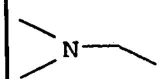
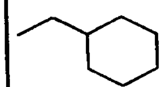
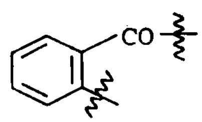
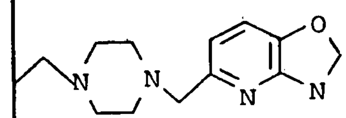
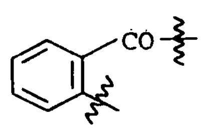
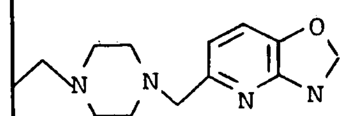
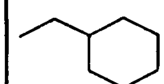
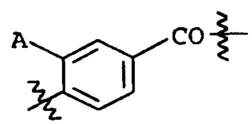
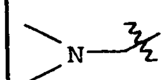
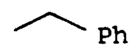
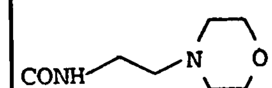
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
75	Naphtha	SO_2NH	H				H
76		SO_2NH	H				H
77		SO_2NH	H				$CONH_2$
78		SO_2NH	H				$CONH_2$
79		SO_2NH	H				$CONH_2$

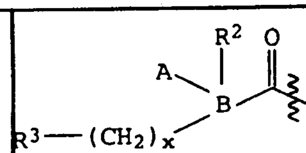
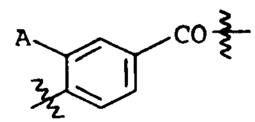
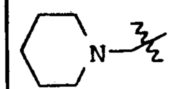
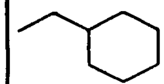
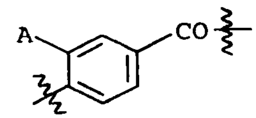
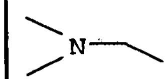
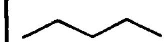
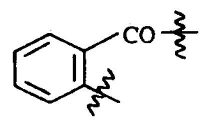
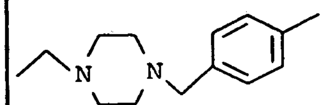
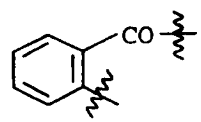
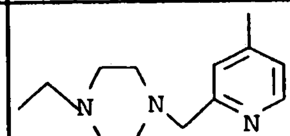
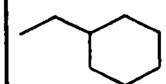
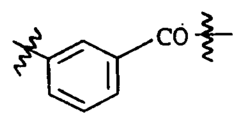
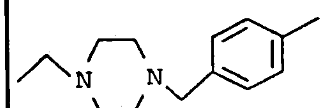
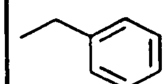
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
80	Naphth	CONH	MeO				H
81	Naphth	SO_2NH	H				$CONH_2$
82	Naphth	SO_2NH	H				H
83		SO_2NH	H				$CONH_2$
84		SO_2NH	H				$CONH_2$

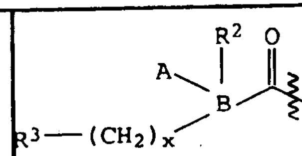
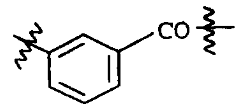
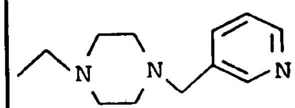
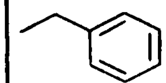
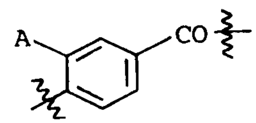
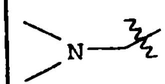
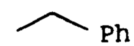
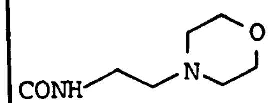
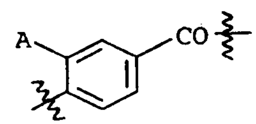
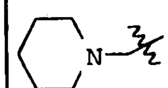
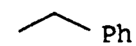
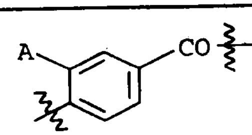
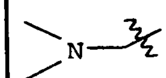
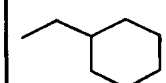
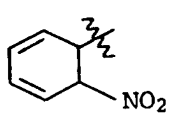
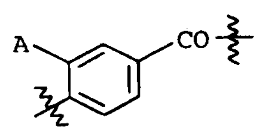
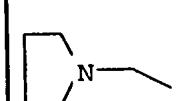
Nr.	R1	A	R2		R3—(CH2)x—	R4	R5
85	Ph		H				CONH2
86	Ph		H				H
87	Ph		H				H
88	Ph		H				CONH2
89	Ph	SO_2NH	H				CONH2

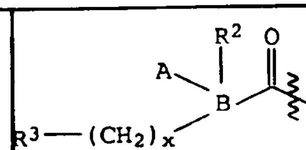
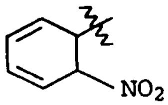
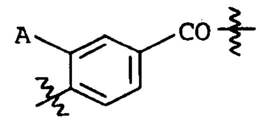
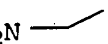
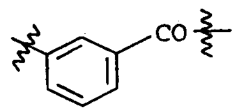
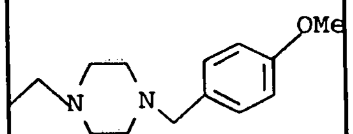
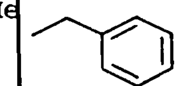
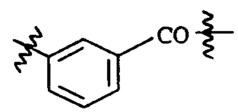
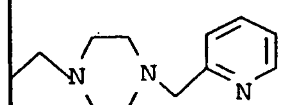
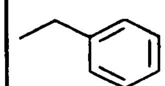
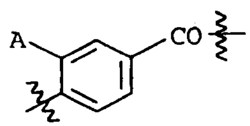
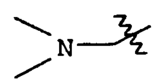
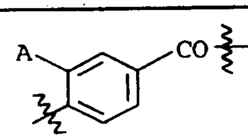
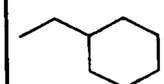
Nr.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
90	Naphth	SO_2NH	H				H
91	2-Py	SO_2NH	H			 Ph	H
92	2-Py	SO_2NH	H			 Ph	$CONH_2$
93		SO_2NH	H		Me_2N 		$CONH_2$
94		SO_2NH	H		Et_2N 		H

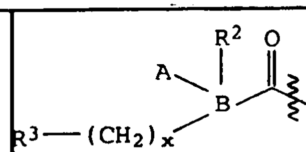
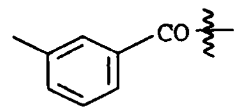
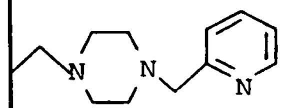
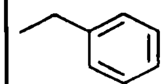
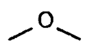
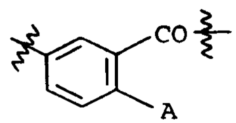
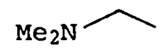
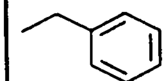
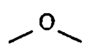
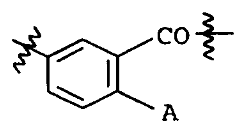
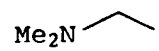
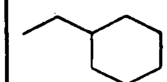
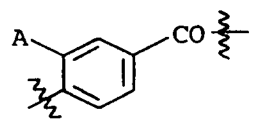
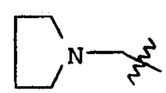
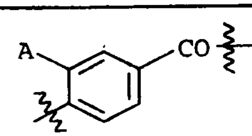
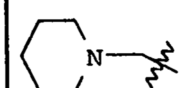
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
95		SO_2NH	H				$CONH_2$
96		SO_2NH	H				H
97	H	m=o=O	H				
98	H	m=o=O	H				$CONH_2$
99	Bu	SO_2NH	H				$CONH_2$

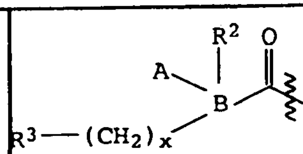
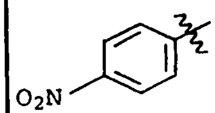
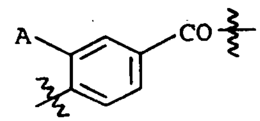
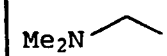
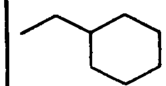
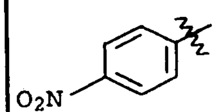
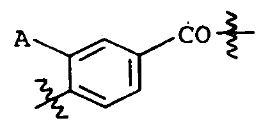
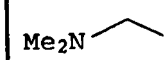
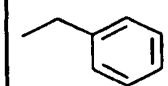
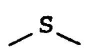
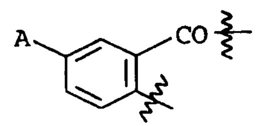
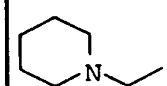
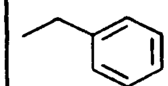
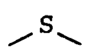
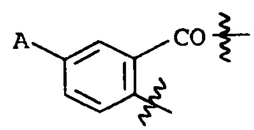
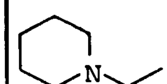
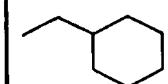
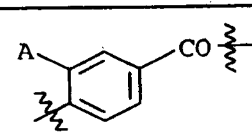
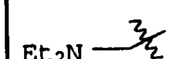
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
100	Ph	SO_2NH	H				H
101	2-Py	SO_2NH	H				$CONH_2$
102	H	m=o=O	H				H
103	H	m=o=O	H				H
104	Bu	SO_2NH	H				

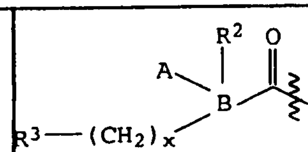
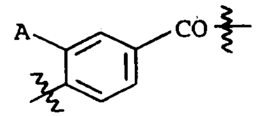
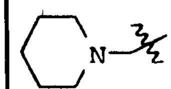
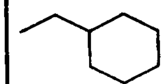
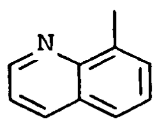
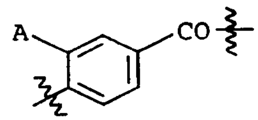
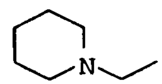
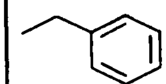
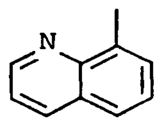
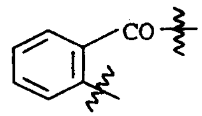
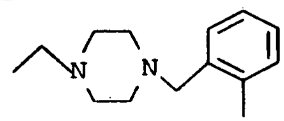
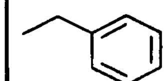
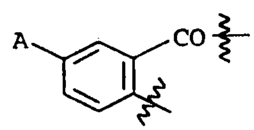
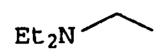
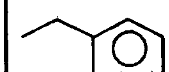
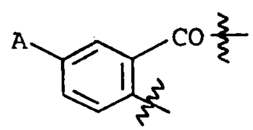
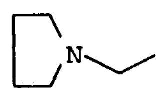
Nr.	R^1	A	R^2		R^3—(CH$_2$)$_x$—	R^4	R^5
105	Ph	SO_2NH	H				H
106	2-Py	SO_2NH	H				$CONH_2$
107	H	m=o=O	H			 Ph	$CONH_2$
108	H	m=o=O	H				$CONH_2$
109	H	m=o=O	H				H

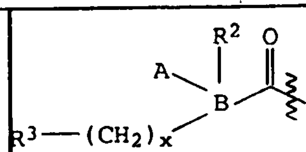
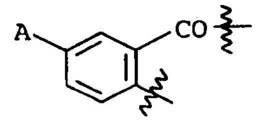
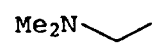
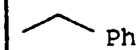
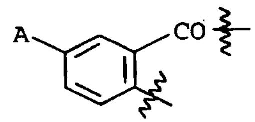
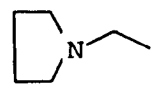
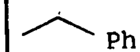
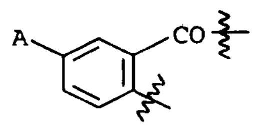
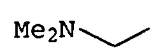
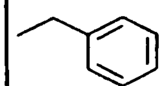
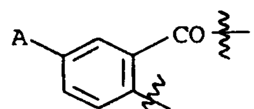
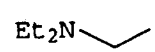
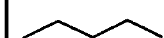
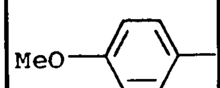
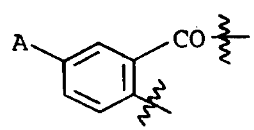
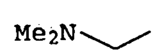
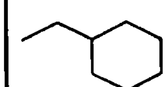
Nr.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
110	H	m=o=O	H				H
111	Ph	SO_2NH	H				
112	Ph	SO_2NH	H				$CONH_2$
113	2-Py	SO_2NH	H				H
114		SO_2NH	H				$CONH_2$

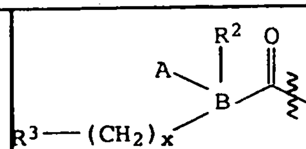
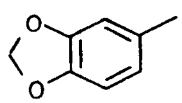
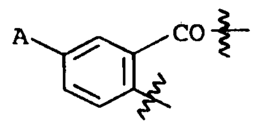
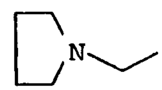
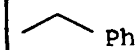
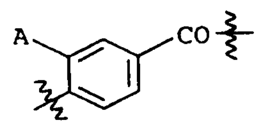
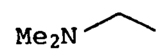
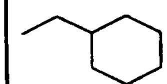
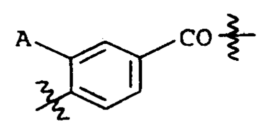
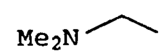
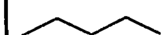
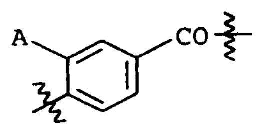
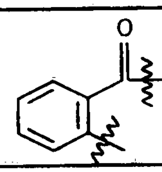
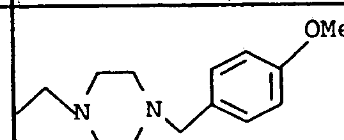
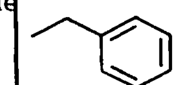
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
115		SO_2NH	H		Et_2N 		H
116	H	m=o=O	H				H
117	H	m=o=O	H				H
118	Ph	SO_2NH	H			 Ph	H
119	Naphth	SO_2NH	H		Et_2N 		$CONH_2$

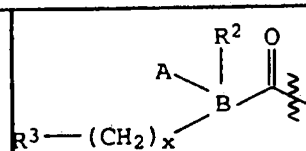
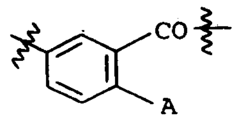
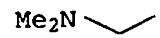
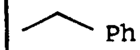
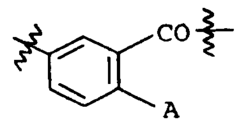
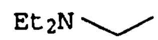
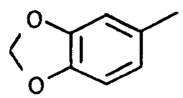
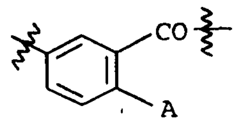
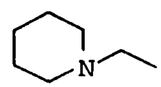
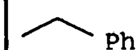
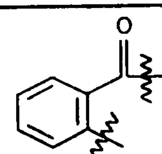
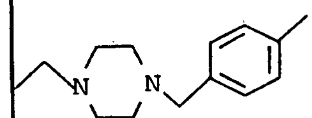
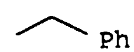
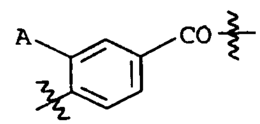
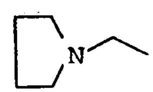
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
120	H	$SONH_2$	H				H
121	Ph		H				H
122	Ph		H				H
123	Ph	SO_2NH	H				H
124	Naphth	SO_2NH	H				$CONH_2$

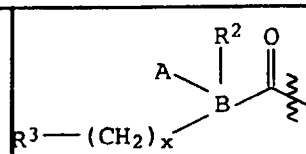
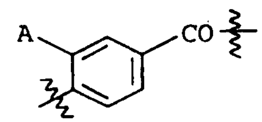
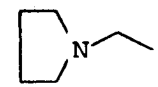
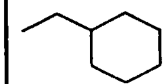
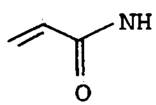
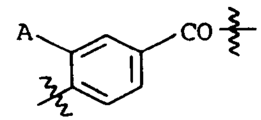
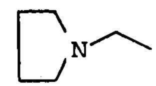
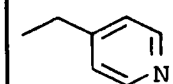
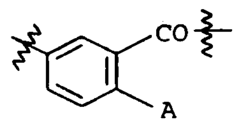
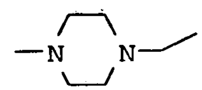
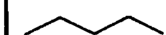
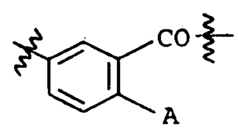
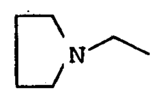
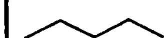
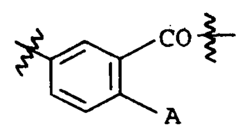
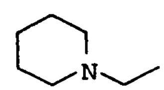
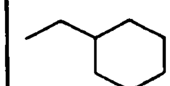
Nr.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
125		SO_2NH	H				H
126		SO_2NH	H				$CONH_2$
127	Ph		H				$CONH_2$
128	Ph		H				$CONH_2$
129	Bu	SO_2NH	H				H

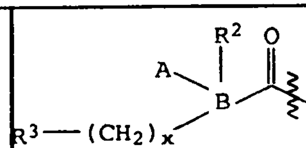
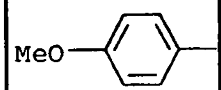
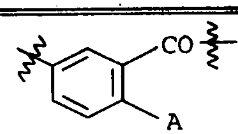
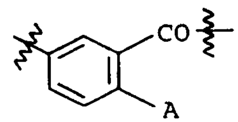
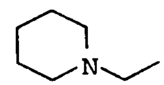
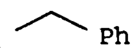
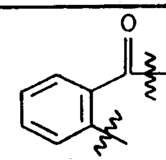
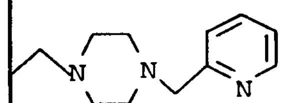
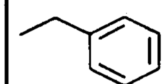
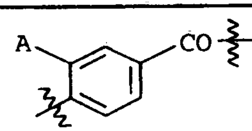
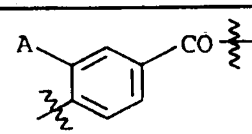
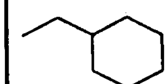
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
130	Ph	SO_2NH	H				$CONH_2$
131		SO_2NH	H				$CONH_2$
132		m=o=O	H				$CONH_2$
133	Ph	CH_2O	H				$CONH_2$
134	2-Py	CH_2O	H				$CONH_2$

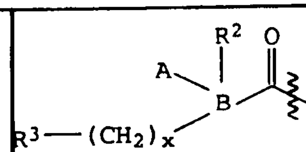
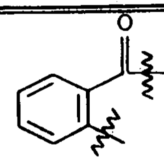
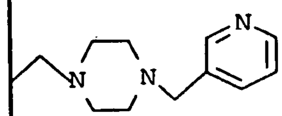
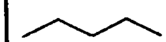
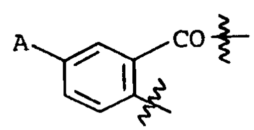
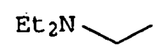
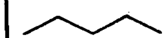
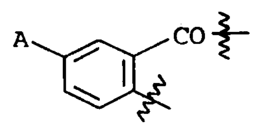
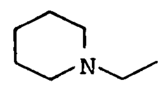
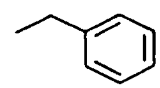
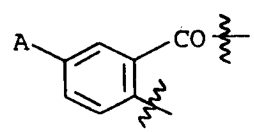
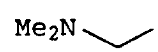
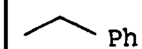
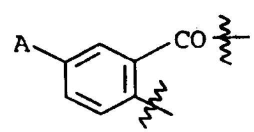
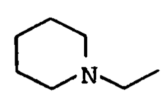
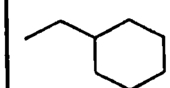
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
135	3-Py	CH_2O	H				$CONH_2$
136	4-Py	CH_2O	H				H
137	2-Tol	CH_2O	H				H
138	3-Tol	CH_2O	H				H
139		CH_2O	H				$CONH_2$

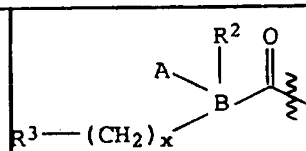
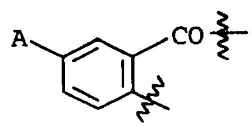
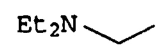
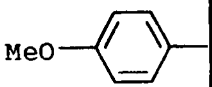
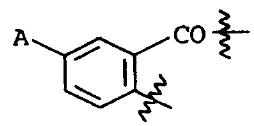
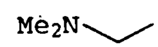
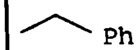
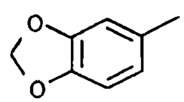
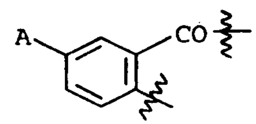
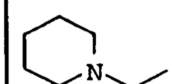
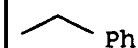
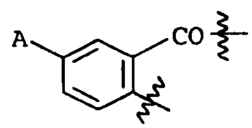
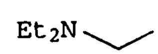
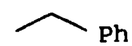
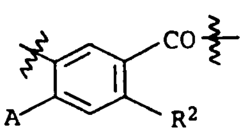
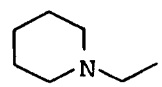
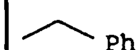
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
140		CH_2O	H				H
141	Ph	$CONH_2$	H				$CONH_2$
142	Naphth	$CONH_2$	H				$CONH_2$
143	Naphth	$CONH_2$	H		Et_2N		$CONH_2$
144	H	m=o=O	H				$CONH_2$

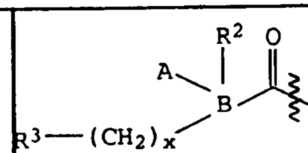
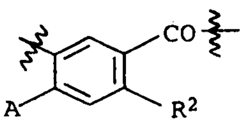
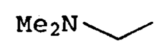
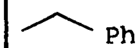
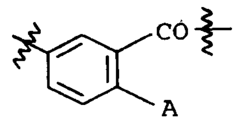
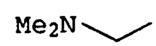
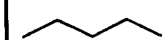
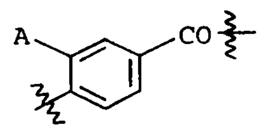
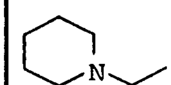
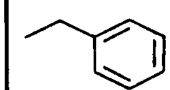
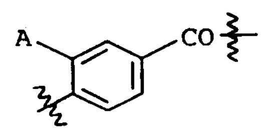
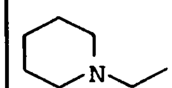
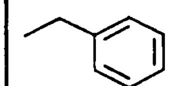
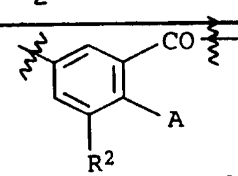
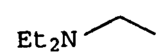
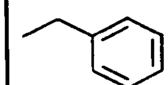
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
145	2-Py	CH_2O	H				H
146	3-Py	CH_2O	H				$CONH_2$
147		CH_2O	H				H
148	H	m=o=O	H				H
149	Ph	CONH	H				H

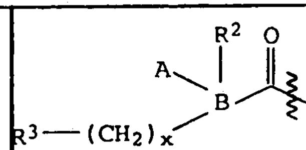
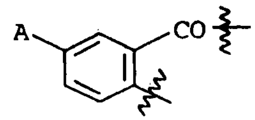
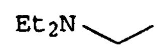
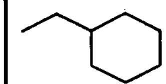
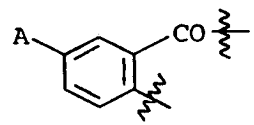
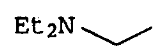
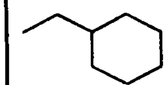
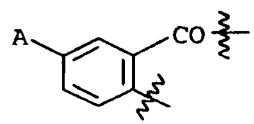
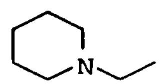
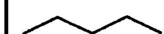
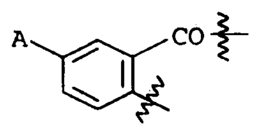
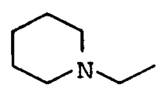
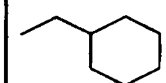
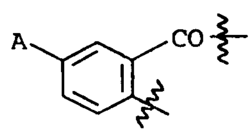
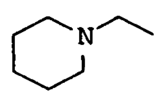
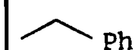
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
150	Naphth	CONH	H				H
151	Ph		H				H
152	4-Py	CH_2O	H				$CONH_2$
153	2-Tol	CH_2O	H				H
154	3-Tol	CH_2O	H				$CONH_2$

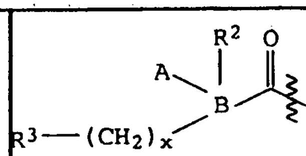
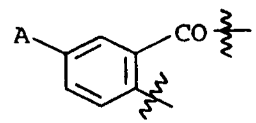
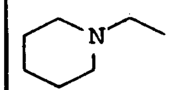
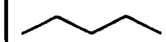
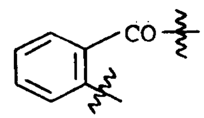
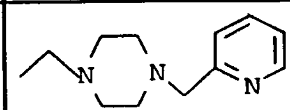
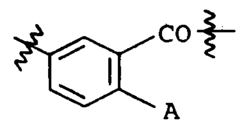
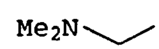
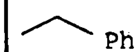
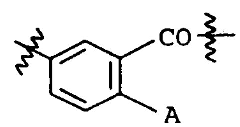
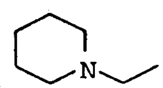
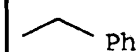
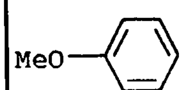
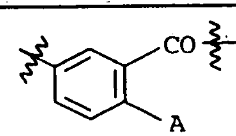
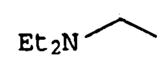
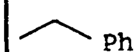
Nr.	R1	A	R2		R3—(CH2)x—	R4	R5
155		CH_2O	H				H
156	Ph	CH_2O	H				$CONH_2$
157	H	m=o=O	H				$CONH_2$
158	Naphth	CONH	H		Me_2N		H
159	Ph	CONH	H		Me_2N		$CONH_2$

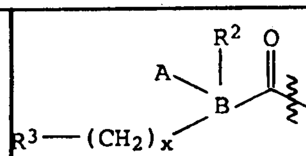
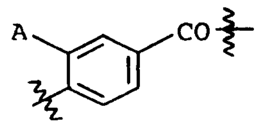
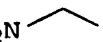
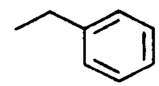
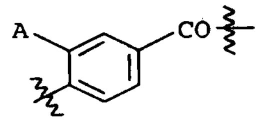
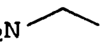
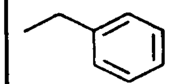
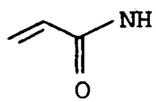
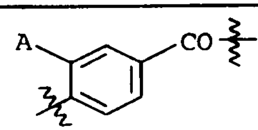
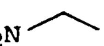
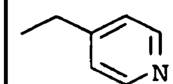
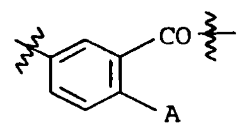
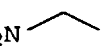
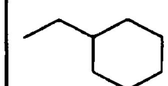
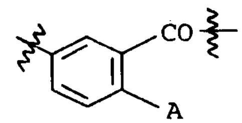
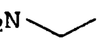
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
160	H	m=o=O	H				H
161	Ph	CH_2O	H				H
162	2-Py	CH_2O	H				H
163	2-Tol	CH_2O	H				$CONH_2$
164	3-Py	CH_2O	H				H

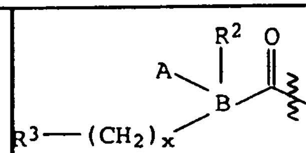
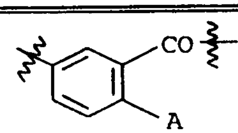
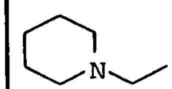
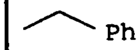
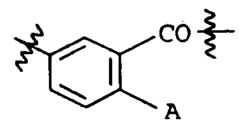
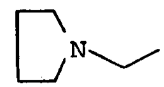
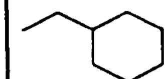
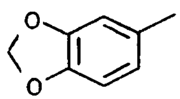
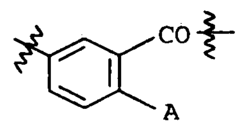
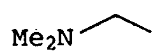
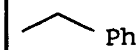
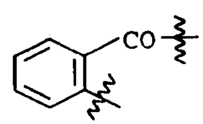
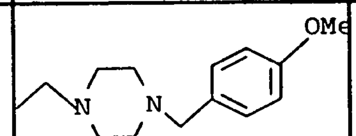
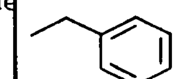
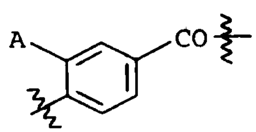
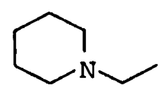
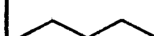
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
165	3-Tol	CH_2O	H				$CONH_2$
166		CH_2O	H				H
167		CH_2O	H				H
168	4-Py	CH_2O	H				$CONH_2$
169	Ph	SO_2NH	MeO				H

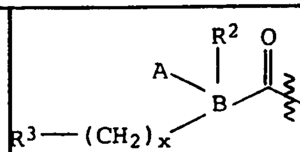
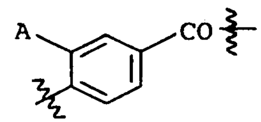
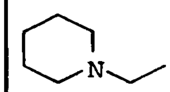
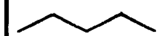
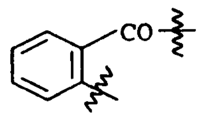
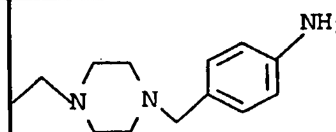
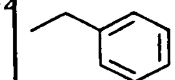
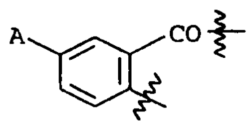
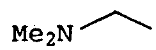
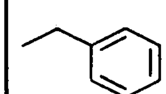
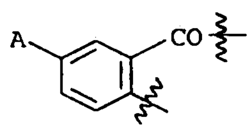
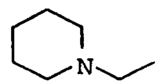
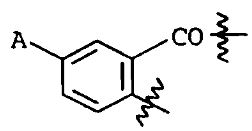
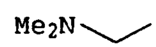
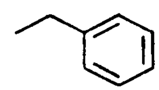
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
170	Naphth	SO_2NH	MeO				H
171	3-Tol	CH_2O	H				$CONH_2$
172	Ph	CONH	H				H
173	Naphth	CONH	H				H
174	Bu	SO_2NH	Et				$CONH_2$

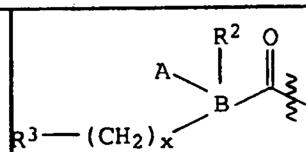
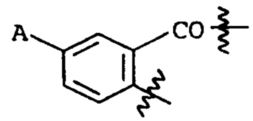
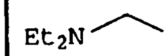
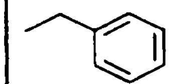
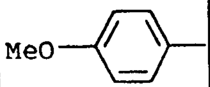
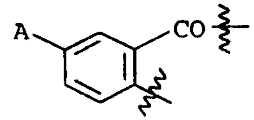
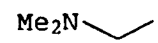
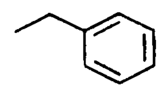
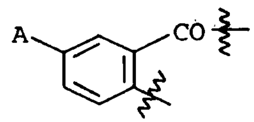
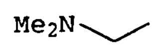
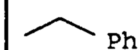
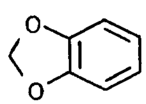
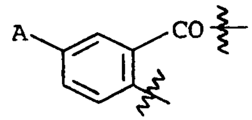
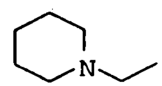
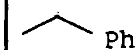
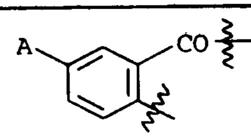
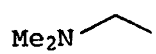
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
175	3-Tol	CH_2O	H				H
176	3-Tol	CH_2O	H				$CONH_2$
177	4-Py	CH_2O	H				H
178	4-Py	CH_2O	H				H
179	Ph	CH_2O	H				$CONH_2$

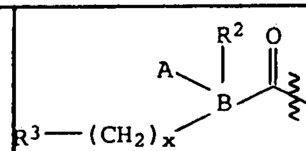
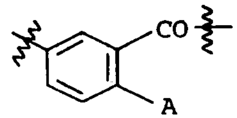
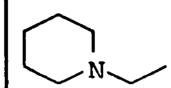
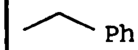
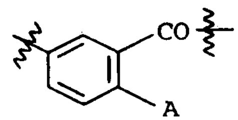
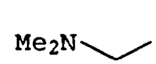
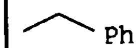
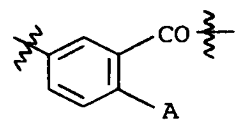
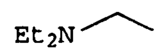
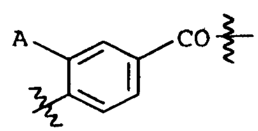
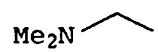
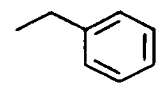
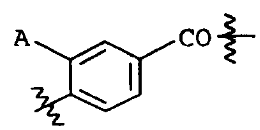
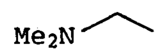
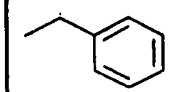
Nr.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
180	Ph	CH_2O	H				$CONH_2$
181	H	m=o=O	H				$CONH_2$
182	Ph	CH_2O	H				$CONH_2$
183	2-Py	CH_2O	H				H
184		CH_2O	H				$CONH_2$

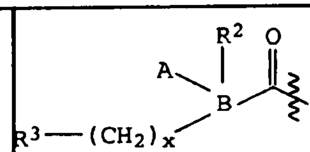
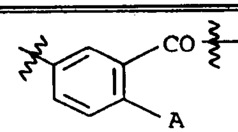
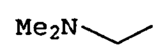
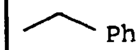
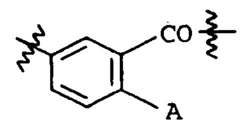
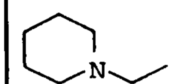
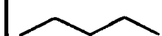
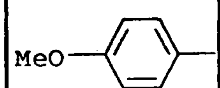
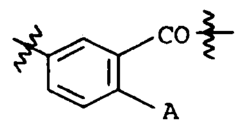
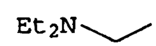
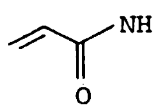
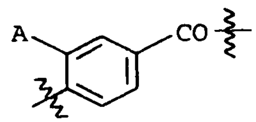
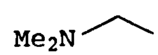
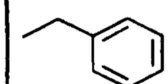
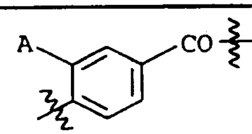
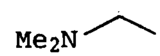
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
185	Ph	CONH	H		Me_2N 		$CONH_2$
186	Naphth	CONH	H		Me_2N 		H
187	Ph		H		Me_2N 		H
188	3-Py	CH_2O	H		Et_2N 		H
189	3-Tol	CH_2O	H		Me_2N 	 Ph	H

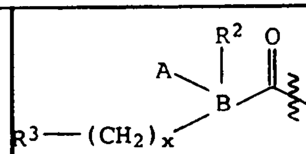
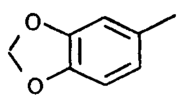
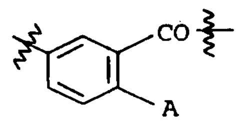
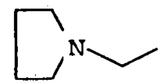
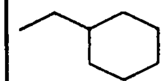
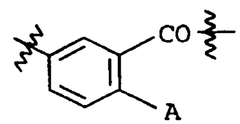
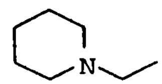
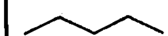
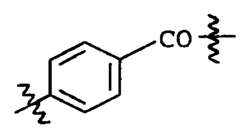
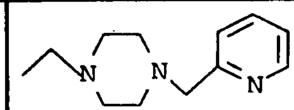
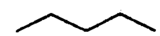
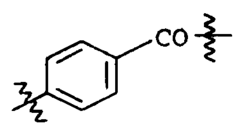
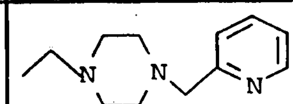
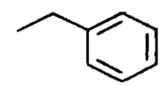
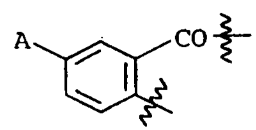
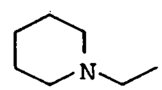
Nr.	R1	A	R2		R3—(CH2)x—	R4	R5
190	4-Py	CH_2O	H				$CONH_2$
191	2-Tol	CH_2O	H				$CONH_2$
192		CH_2O	H				H
193	H	m=o=O	H				H
194	Ph	CONH	H				$CONH_2$

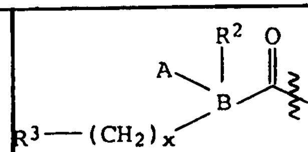
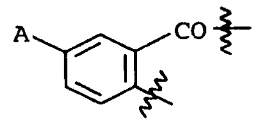
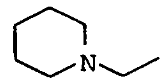
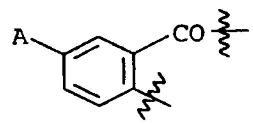
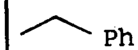
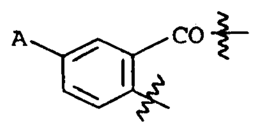
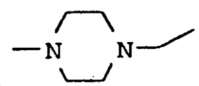
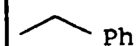
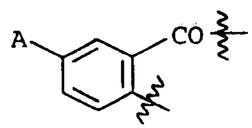
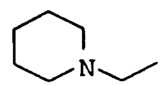
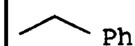
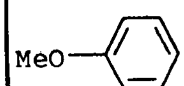
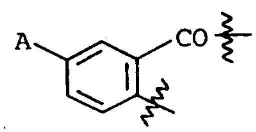
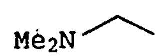
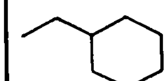
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
195	Naphth	CONH	H				$CONH_2$
196	H	m=o=O	H				$CONH_2$
197	2-Py	CH_2O	H				H
198	3-Py	CH_2O	H				$CONH_2$
199	3-Tol	CH_2O	H				$CONH_2$

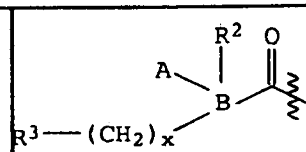
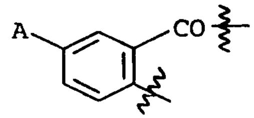
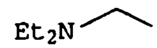
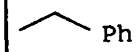
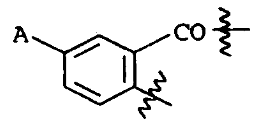
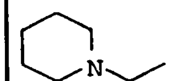
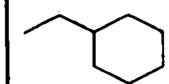
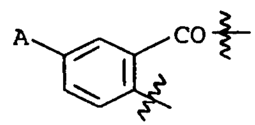
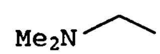
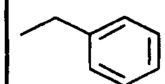
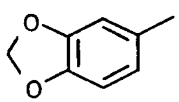
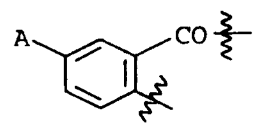
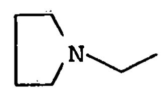
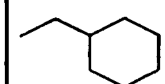
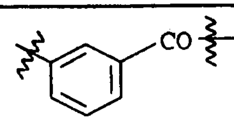
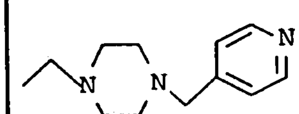
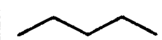
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
200	Ph	CH_2O	H				H
201		CH_2O	H				$CONH_2$
202	4-Py	CH_2O	H				H
203		CH_2O	H				$CONH_2$
204	2-Py	CH_2O	H				$CONH_2$

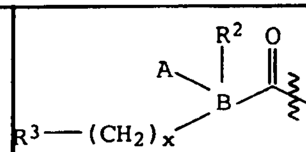
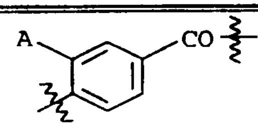
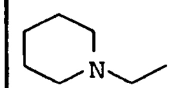
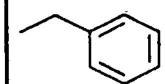
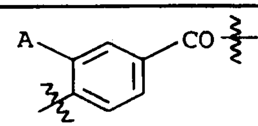
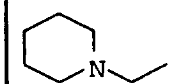
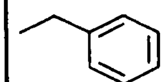
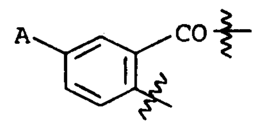
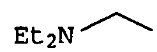
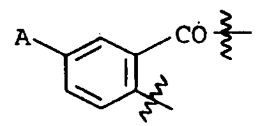
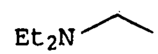
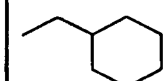
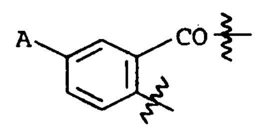
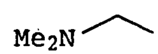
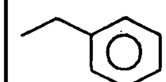
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
205	Ph	CH_2O	H				H
206	2-Py	CH_2O	H				$CONH_2$
207	2-Tol	CH_2O	H				H
208	Ph	CONH	H				H
209	Naphth	CONH	H				$CONH_2$

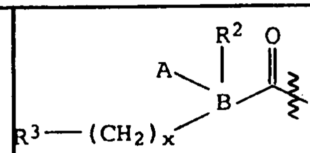
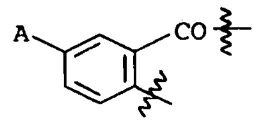
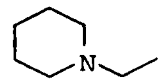
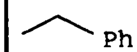
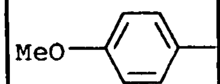
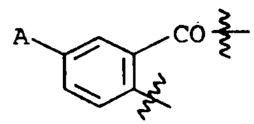
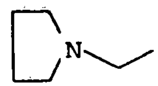
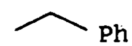
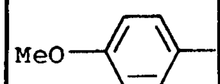
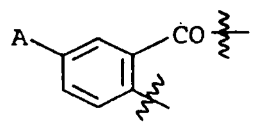
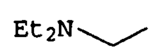
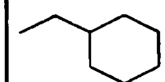
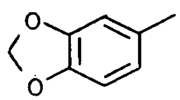
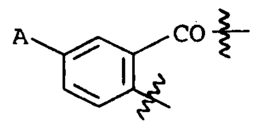
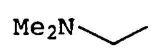
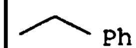
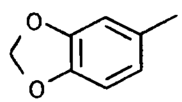
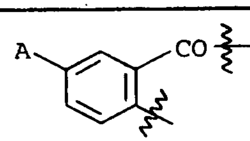
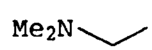
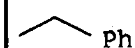
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
210	3-Py	CH_2O	H				H
211	4-Py	CH_2O	H				H
212		CH_2O	H				$CONH_2$
213	Ph		H				$CONH_2$
214	Ph	CONH	H				$CONH_2$

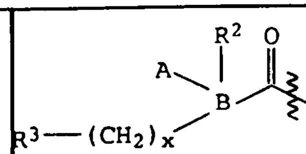
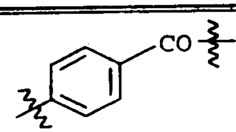
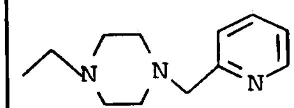
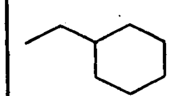
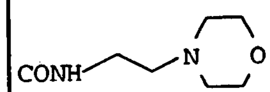
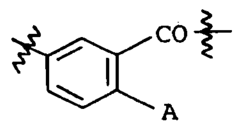
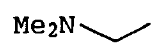
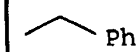
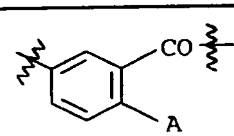
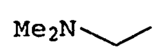
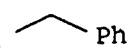
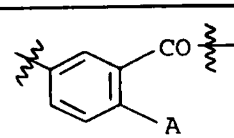
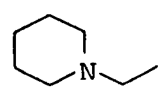
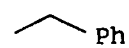
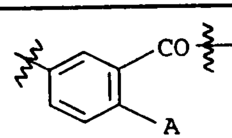
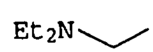
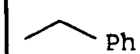
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
215		CH_2O	H				$CONH_2$
216	3-Tol	CH_2O	H				H
217	H	m=o=O	H				$CONH_2$
218	H	m=o=O	H				H
219	2-Py	CH_2O	H				H

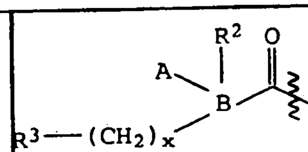
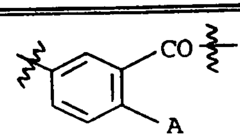
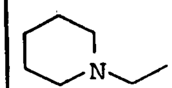
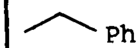
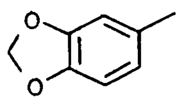
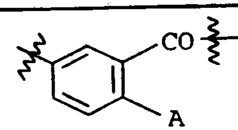
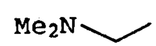
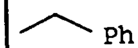
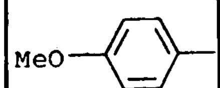
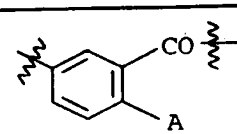
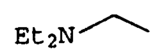
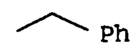
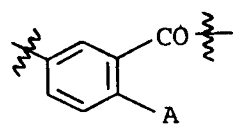
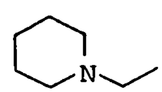
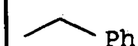
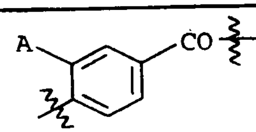
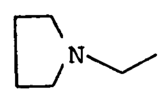
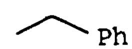
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
220	3-Py	CH_2O	H				H
221	2-Tol	CH_2O	H				$CONH_2$
222	4-Tol	CH_2O	H				$CONH_2$
223	4-Py	CH_2O	H				$CONH_2$
224		CH_2O	H				H

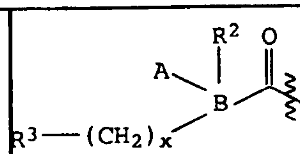
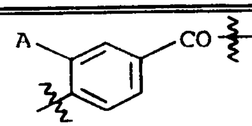
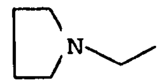
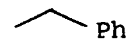
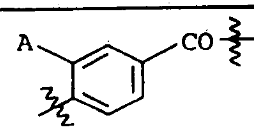
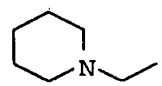
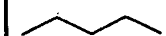
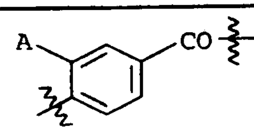
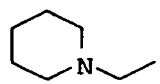
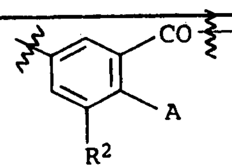
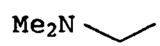
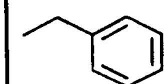
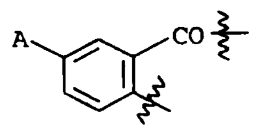
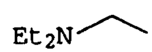
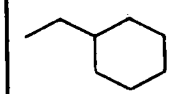
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
225	4-Py	CH_2O	H				H
226	Ph	CH_2O	H				$CONH_2$
227	3-Tol	CH_2O	H				H
228		CH_2O	H				H
229	H	m=o=O	H				$CONH_2$

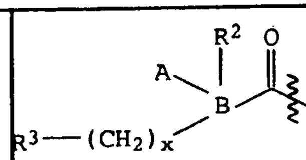
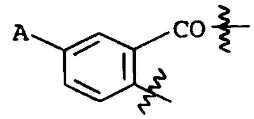
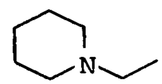
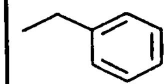
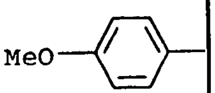
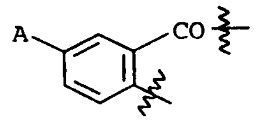
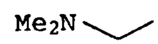
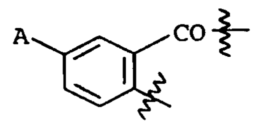
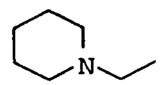
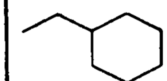
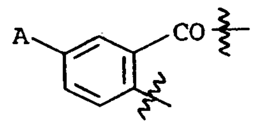
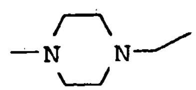
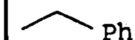
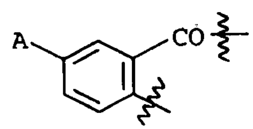
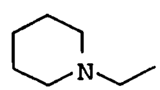
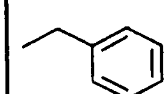
Nr.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
230	Ph	CONH	H				$CONH_2$
231	Naphth	CONH	H				$CONH_2$
232	2-Tol	CH_2O	H				H
233	2-Tol	CH_2O	H				$CONH_2$
234	3-Py	CH_2O	H				H

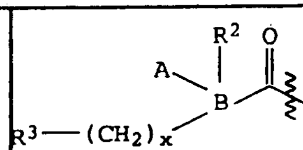
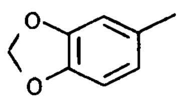
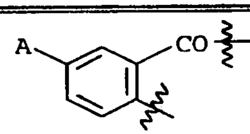
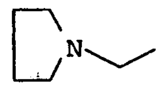
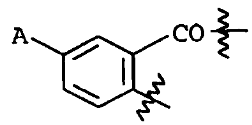
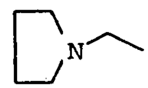
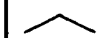
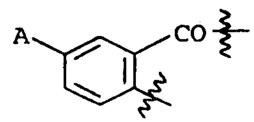
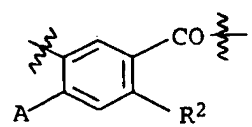
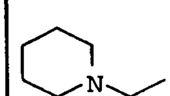
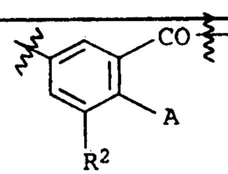
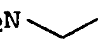
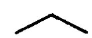
Nr.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
235	Ph	CH_2O	H				$CONH_2$
236		CH_2O	H				H
237		CH_2O	H				H
238		CH_2O	H				H
239		CH_2O	H				$CONH_2$

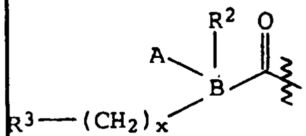
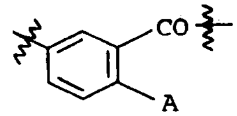
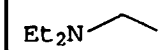
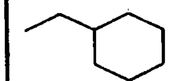
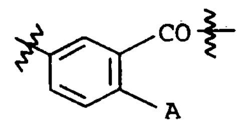
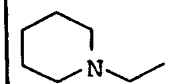
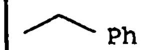
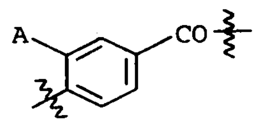
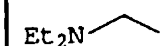
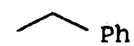
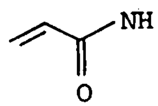
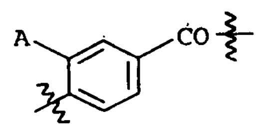
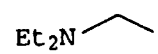
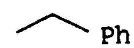
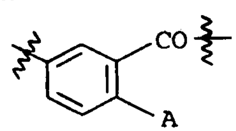
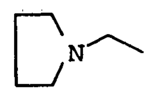
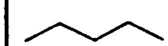
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
240	H	m=o=O	H				
241	Ph	CH_2O	H				H
242	3-Py	CH_2O	H				$CONH_2$
243	4-Py	CH_2O	H				H
244	2-Tol	CH_2O	H				H

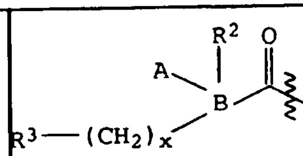
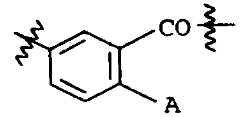
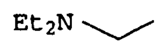
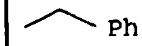
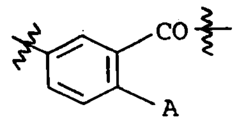
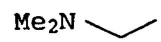
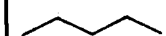
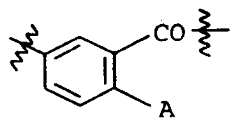
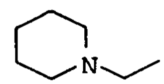
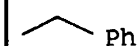
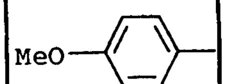
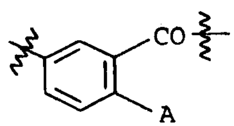
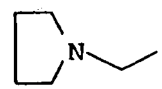
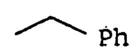
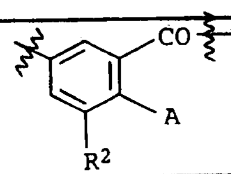
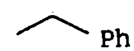
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
245	3-Tol	CH_2O	H				$CONH_2$
246		CH_2O	H				H
247		CH_2O	H				H
248	2-Py	CH_2O	H				$CONH_2$
249	Ph	CONH	H				H

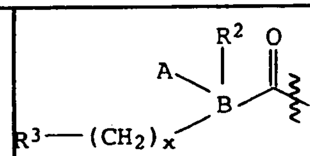
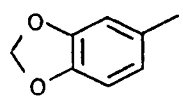
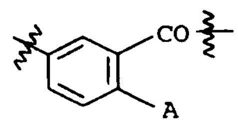
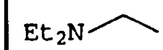
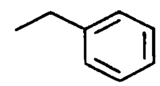
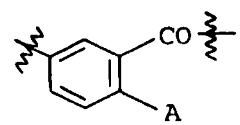
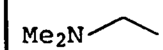
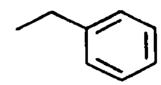
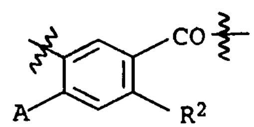
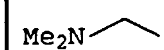
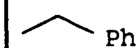
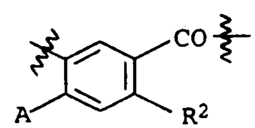
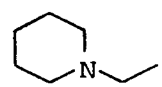
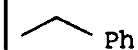
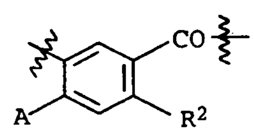
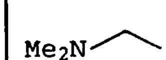
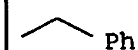
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
250	Ph	CONH	H				$CONH_2$
251	Ph	CONH	H				H
252	Naphth	CONH	H				H
253	Ph	SO_2NH	Et				H
254	Ph	CH_2O	H				H

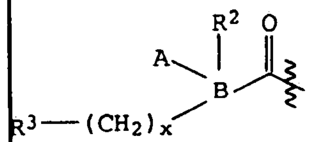
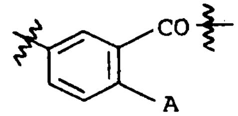
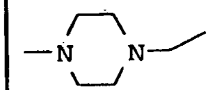
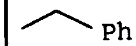
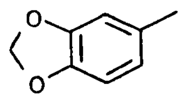
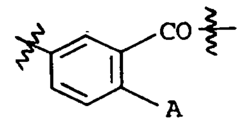
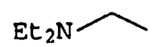
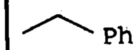
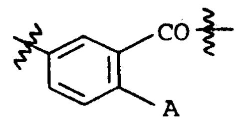
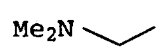
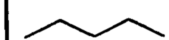
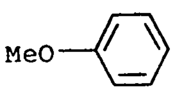
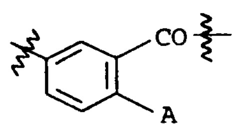
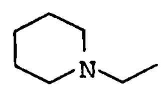
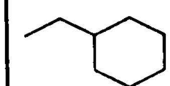
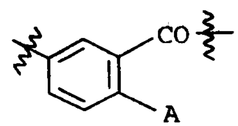
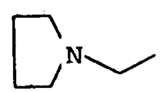
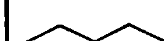
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
255	2-Py	CH_2O	H				$CONH_2$
256		CH_2O	H				H
257	3-Py	CH_2O	H				$CONH_2$
258	2-Tol	CH_2O	H				$CONH_2$
259	3-Tol	CH_2O	H				$CONH_2$

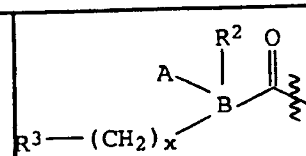
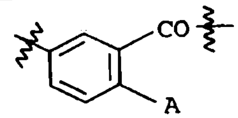
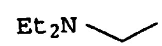
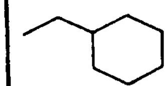
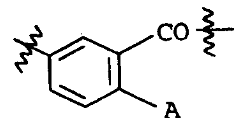
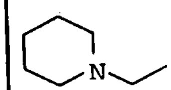
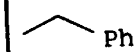
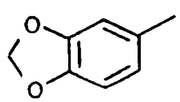
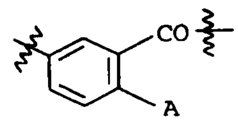
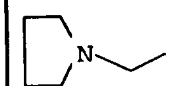
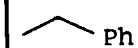
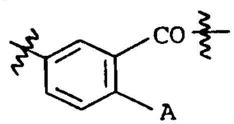
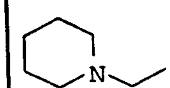
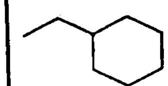
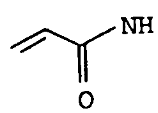
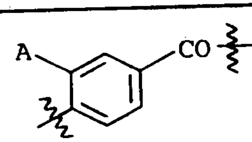
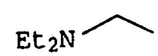
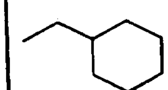
Nr.	R1	A	R2		R3—(CH2)x—	R4	R5
260		CH_2O	H				H
261	4-Py	CH_2O	H			 Ph	$CONH_2$
262	Ph	CH_2O	H		Me_2N 	 Ph	H
263	Bu	SO_2NH	MeO			 Ph	H
264	Naphth	SO_2NH	Et		Et_2N 	 Ph	H

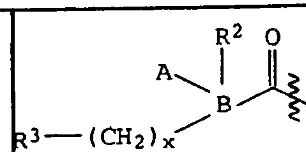
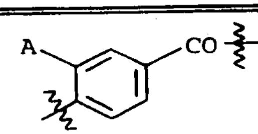
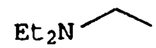
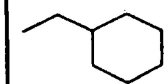
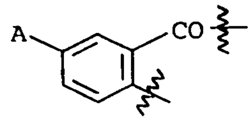
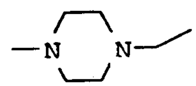
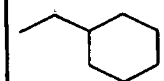
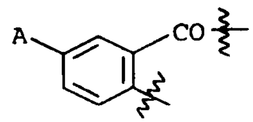
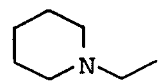
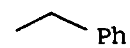
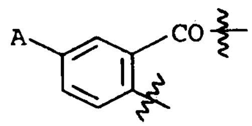
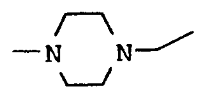
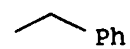
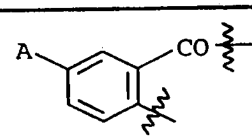
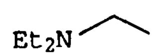
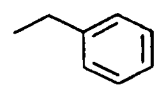
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
265	4-Py	CH_2O	H				$CONH_2$
266	3-Tol	CH_2O	H				H
267	Ph	CONH	H				$CONH_2$
268	Ph		H				$CONH_2$
269	2-Py	CH_2O	H				$CONH_2$

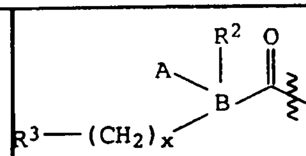
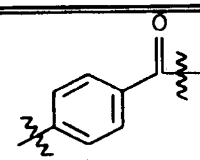
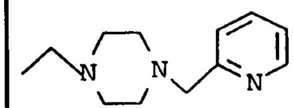
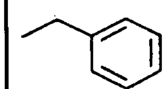
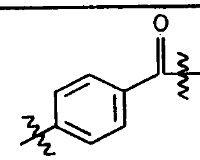
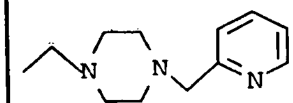
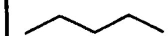
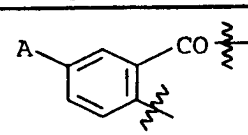
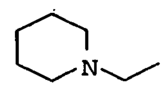
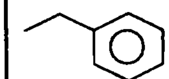
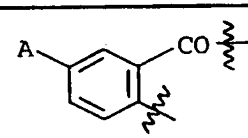
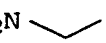
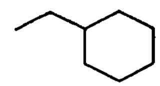
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
270	2-Tol	CH_2O	H				$CONH_2$
271	Ph	CH_2O	H				H
272	3-Py	CH_2O	H				$CONH_2$
273		CH_2O	H				$CONH_2$
274	Ph	SO_2NH	Et				H

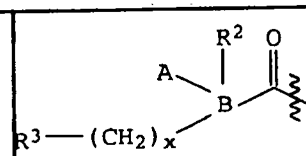
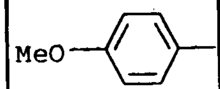
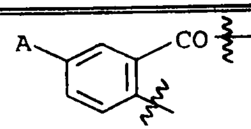
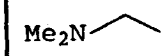
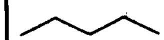
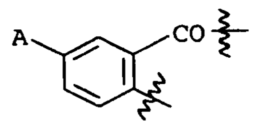
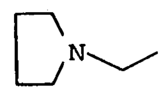
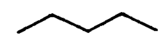
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
275		CH_2O	H				$CONH_2$
276	Naphth	SO_2NH	Et				$CONH_2$
277	Ph	SO_2NH	MeO				H
278	Naphth	SO_2NH	MeO				H
279	Bu	SO_2NH	MeO				H

Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
280	Ph	CH_2O	H				$CONH_2$
281		CH_2O	H				H
282	Ph	CH_2O	H				$CONH_2$
283		CH_2O	H				H
284	2-Py	CH_2O	H				H

Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
285	2-Py	CH_2O	H				$CONH_2$
286	3-Py	CH_2O	H				H
287		CH_2O	H				$CONH_2$
288	2-Tol	CH_2O	H				H
289	Ph		H				$CONH_2$

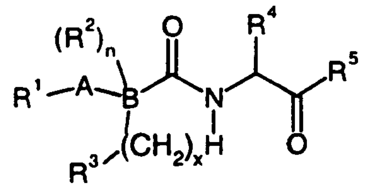
Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
290	Ph	CONH	H				$CONH_2$
291	4-Py	CH_2O	H				H
292	4-Py	CH_2O	H				$CONH_2$
293	3-Tol	CH_2O	H				$CONH_2$
294	2-Tol	CH_2O	H				$CONH_2$

Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
295	H	m=o=O	H				H
296	H	m=o=O	H				H
297	3-Tol	CH_2O	H				H
298	2-Py	CH_2O	H		Me_2N 		H

Nr.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
299		CH_2O	H				$CONH_2$
298	2-Tol	CH_2O	H				H

Patentansprüche

1. Amide der allgemeinen Formel I

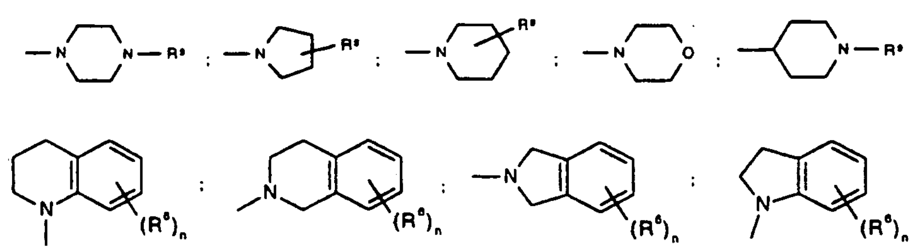


und ihre tautomeren und isomeren Formen, möglichen enantiomeren und diastereomeren Formen, sowie mögliche physiologisch verträgliche Salze, worin die Variablen folgende Bedeutung haben:

R^1 Wasserstoff, C_1-C_6-Alkyl, verzweigt und unverzweigt, Phenyl, Naphthyl, Chinolinyl, Pyridyl, Pyrimidyl, Pyrazyl, Pyridazyl, Chinazolyl, Chinoxalyl, Thienyl, Benzothienyl, Benzofuranyl, Furanyl, und Indolyl bedeuten kann, wobei die Ringe noch mit zu bis 3 Resten R^6 substituiert sein können, und

R^2 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, O-C_1-C_6-Alkyl, verzweigt oder unverzweigt, C_2-C_6-Alkenyl, C_2-C_6-Alkinyl, C_1-C_6-Alkyl-Phenyl, C_2-C_6-Alkenyl-Phenyl, C_2-C_6-Alkinyl-Phenyl, OH, Cl, F, Br, J, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-Alkyl, NHCO-C_1-C_4-Alkyl, NHCO-Phenyl, $CONHR^9$, $NHSO_2$-C_1-C_4-Alkyl, $NHSO_2$-Phenyl, SO_2-C_1-C_4-Alkyl und SO_2-Phenyl bedeuten und

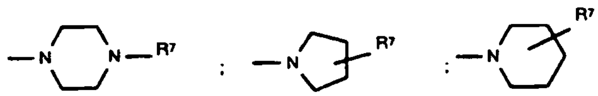
R^3 NR^7R^8 oder einen Ring darstellen kann wie



R^4 -C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Phenyl-, Pyridyl-, Thienyl-, Cyclohexyl-, Indolyl- oder Naphthyl-Ring tragen kann, der seinerseits mit maximal zwei Resten R^6 substituiert ist, und

302/98 Dp/AS

R^5 Wasserstoff, $COOR^{11}$ und CO-Z bedeutet, worin Z $NR^{12}R^{13}$ und



bedeutet und

R^6 Wasserstoff, C_1-C_4-Alkyl, verzweigt oder unverzweigt, -O-C_1-C_4- Alkyl, OH, Cl, F, Br, J, CF_3, NO_2 , NH_2 , CN , COOH , COO-C_1-C_4-Alkyl, -NHCO-C_1-C_4-Alkyl, -NHCO-Phenyl, -$NHSO_2$-C_1-C_4-Alkyl, -$NHSO_2$-Phenyl, -SO_2-C_1-C_4-Alkyl und -SO_2-Phenyl bedeutet und

R^7 Wasserstoff, C_1-C_6-Alkyl, geradlinig oder verzweigt, bedeutet und das mit einem Phenylring substituiert kann, der selbst noch mit einem oder zwei Resten R^{10} substituiert sein kann, und

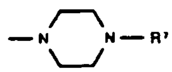
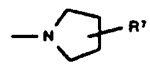
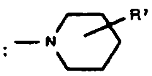
R^8 Wasserstoff, C_1-C_6-Alkyl, geradlinig oder verzweigt, bedeutet und das mit einem Phenylring substituiert kann, der selbst noch mit einem oder zwei Resten R^{10} substituiert sein kann, und

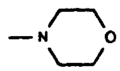
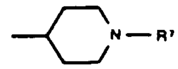
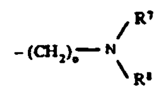
R^9 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Substituenten R^{16} tragen kann, Phenyl, Pyridyl, Pyrimidyl, Pyridazyl, Pyrazinyl, Pyrazyl, Naphthyl, Chinolinyl, Imidazolyl, das noch einen oder zwei Substituenten R^{14} tragen kann, und

R^{10} Wasserstoff, C_1-C_4-Alkyl, verzweigt oder unverzweigt, -O-C_1-C_4-Alkyl, OH Cl, F, Br, J, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-Alkyl, -NHCO-C_1-C_4-Alkyl, -NHCO-Phenyl, -$NHSO_2$-C_1-C_4-Alkyl, -$NHSO_2$-Phenyl, -SO_2-C_1-C_4-Alkyl und -SO_2-Phenyl bedeuten kann

R^{11} Wasserstoff, C_1-C_6-Alkyl, geradlinig oder verzweigt, bedeutet und das mit einem Phenylring substituiert kann, der selbst noch mit einem oder zwei Resten R^{10} substituiert sein kann, und

R^{12} Wasserstoff, C_1-C_6-Alkyl, verzweigt und unverzweigt, bedeutet, und

 ;  ;  ; 

 ;  

R^{13} Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch mit einem Phenylring, der noch einen Rest R^{10} tragen kann, und mit

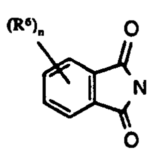
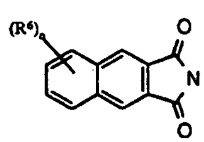
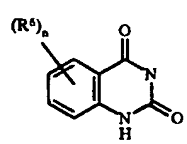
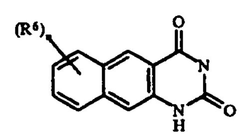
substituiert sein kann bedeutet, und

R^{14} Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, O-C_1-C_6-Alkyl, verzweigt oder unverzweigt, OH, Cl, F, Br, J, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-Alkyl bedeutet oder zwei Reste R^{14} eine Brücke $OC(R^{15})_2O$ darstellen kann und

R^{15} Wasserstoff, C_1-C_6-Alkyl, verzweigt und unverzweigt, bedeutet und

R^{16} ein Phenyl-, Pyridyl-, Pyrimidyl-, Pyridazyl-, Pyrazinyl-, Pyrazyl-, Pyrrolyl-, Naphthyl-, Chinolinyl-, Imidazolyl-Ring sein kann, der noch einen oder zwei Substituenten R^6 tragen kann, und

A $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-(CH_2)_o-SO-(CH_2)_m-$, $-(CH_2)_o-SO_2-(CH_2)_m-$, $-CH{=}CH-$, $-C{\equiv}C-$, $-CO-CH{=}CH-$, $-(CH_2)_o-CO-(CH_2)_m-$, $-(CH_2)_m-NHCO-(CH_2)_o-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-NHSO_2-(CH_2)_o-$, $-NH-CO-CH{=}CH-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$, $-CH{=}CH-CONH-$ und bedeutet,

 ,  ,  und 

R^1–A zusammen auch

bedeuten und

B Phenyl, Pyridin, Pyrimidin, Pyrazin, Imidazol und Thiazol bedeutet und

x 1, 2 oder 3 und

n eine Zahl 0, 1 oder 2 bedeutet,und

m, o unabhängig voneinander eine Zahl 0, 1, 2, 3 oder 4 bedeutet.

2. Heterocyclisch substituierte Amide der Formel I gemäß dem Anspruch 1, wobei

B Pyridin oder Phenyl und

R^5 Wasserstoff bedeutet und

R^9 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Substituenten R^{16} tragen

R^{16} Phenyl, der noch einen oder zwei Substituenten R^{14} tragen kann, und

n 0 und 1 und

x 1.

3. Heterocyclisch substituierte Amide der Formel I gemäß dem Anspruch 1, wobei

B Pyridin oder Phenyl und

R^5 $CONR^{12}R^{13}$ bedeutet und

R^9 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Substituenten R^{16} tragen

R^{16} Phenyl, der noch einen oder zwei Substituenten R^{14} tragen kann, und

n 0 und 1 und

x 1.

4. Heterocyclisch substituierte Amide der Formel I gemäß dem Anspruch 1, wobei

B Pyridin oder Phenyl und

R^2 Wasserstoff

R^5 Wasserstoff bedeutet und

R^9 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Substituenten R^{16} tragen

R^{16} Phenyl, der noch einen oder zwei Substituenten R^{14} tragen kann, und

n 0 und 1 und

x 1.

5. Heterocyclisch substituierte Amide der Formel I gemäß dem Anspruch 1, wobei

B Pyridin oder Phenyl und

R^2 Wasserstoff

R^5 $CONR^{12}R^{13}$ bedeutet und

R^9 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Substituenten R^{16} tragen

R^{16} Phenyl, der noch einen oder zwei Substituenten R^{14} tragen kann, und

n 0 und 1 und

x 1.

6. Heterocyclisch substituierte Amide der Formel I gemäß dem Anspruch 1, wobei

A $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-CH{=}CH-$, $-C{\equiv}C-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$ bedeutet und

B Pyridin oder Phenyl und

R^2 Wasserstoff und

R^5 Wasserstoff bedeutet und

R^9 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Substituenten R^{16} tragen kann, und

R^{16} Phenyl und

m, n, o 0 und 1 und

x 1.

7. Heterocyclisch substituierte Amide der Formel I gemäß dem Anspruch 1, wobei

A $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$ bedeutet und

B Pyridin oder Phenyl und

R^2 Wasserstoff

R^5 $CONR^{12}R^{13}$ bedeutet und

R^9 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Substituenten R^{16} tragen kann, und

R^{16} Phenyl und

m, n, o 0 und 1 und

x 1.

8. Heterocyclisch substituierte Amide der Formel I gemäß dem Anspruch 1, wobei

B Pyridin oder Phenyl und

R^1, R^2 Wasserstoff und

R^5 Wasserstoff bedeutet und

R^9 Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Substituenten R^{16} tragen kann, und

R^{16} Phenyl und

m, n, o 0 und

x 1.

9. Heterocyclisch substituierte Amide der Formel I gemäß dem Anspruch 1, wobei

B	Pyridin oder Phenyl und
R^1, R^2	Wasserstoff
R^5	$CONR^{12}R^{13}$ bedeutet und
R^9	Wasserstoff, C_1-C_6-Alkyl, verzweigt oder unverzweigt, das noch einen Substituenten R^{16} tragen kann, und
R^{16}	Phenyl und
m, n, o	0
x	1.

10. Verwendung von Amiden der Formel I gemäß dem Anspruch 1-5 zur Behandlung von Krankheiten.

11. Verwendung von Amiden der Formel I gemäß dem Anspruch 1-5 als Inhibitoren von Cysteinproteasen.

12. Verwendung nach Anspruch 6 als Inhibitoren von Cysteinproteasen wie Calpaine und Cathepsine, insbesondere Calpaine I und II und Cathepsine B und L.

13. Verwendung von Amiden der Formel I gemäß dem Anspruch 1-5 zur Herstellung als Arzneimittel zur Behandlung von Krankheiten, bei denen erhöhte Calpain-Aktivitäten auftreten.

14. Verwendung der Amiden der Formel I gemäß dem Anspruch 1-5 zur Herstellung von Arzneimitteln zur Behandlung von neurodegenerativen Krankheiten und neuronalen Schädigungen.

15. Verwendung nach Anspruch 9 zur Behandlung von solchen neurodegenerativen Krankheiten und neuronalen Schädigungen, die durch Ischämie, Trauma oder Massenblutungen ausgelöst werden.

16. Verwendung nach Anspruch 10 zur Behandlung von Hirnschlag und Schädel-Hirntrauma.

17. Verwendung nach Anspruch 10 zur Behandlung von Alzheimerschen Krankheit und der Huntington-Krankheit.

18. Verwendung nach Anspruch 10 zur Behandlung von Epilepsien.

19. Verwendung der Verbindungen der Formel I gemäß dem Anspruch 1-5 zur Herstellung von Arzneimitteln und Behandlung von Schädigungen des Herzens nach cardialen Ischämien, Schädigungen der Nieren nach renalen Ischämien, Skelettmuskelschädigungen, Muskeldystrophien, Schädigungen, die durch Proliferation der glatten Muskelzellen entstehen, coronarer Vasospasmus, cerebraler Vasospasmus, Katarakten der Augen und Restenosis der Blutbahnen nach Angioplastie.

20. Verwendung der Amiden der Formel I gemäß dem Anspruch 1-5 zur Herstellung von Arzneimitteln zur Behandlung von Tumoren und deren Metastasierung.

21. Verwendung der Amiden der Formel I gemäß dem Anspruch 1-5 zur Herstellung von Arzneimitteln zur Behandlung von Krankheiten, bei denen erhöhte Interleukin-1-Spiegel auftreten.

22. Verwendung der Amide gemäß Anspruch 1-5 zur Behandlung von immunologischen Krankheiten wie Entzündungen und rheumatische Erkrankungen.

23. Arzneimittelzubereitungen zur peroralen, parenteralen und intraperitonalen Anwendung, enthaltend pro Einzeldosis, neben den üblichen Arzneimittelhilfsstoffen, mindestens eines Amides I gemäß Anspruch 1-5.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/02620

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/12 A61K31/50 C07D403/04 C07D317/58 C07D207/06 C07D215/06 C07D215/24 C07D217/04 C07D213/70 C07D213/30 C07C237/32 C07C311/08 C07C311/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 611 756 A (TAKEDA CHEMICAL INDUSTRIES LTD) 24 August 1994 (1994-08-24) see claim 1, page 6 (line 38-54) and page 51 (Ex. 178) ---	1-23
Y	WO 92 12140 A (GEORGIA TECH RES INST) 23 July 1992 (1992-07-23) cited in the application claims 5,10,16 ---	1-23
Y	WO 96 39194 A (ATHENA NEUROSCIENCES INC) 12 December 1996 (1996-12-12) claim 1; example 71 ---	1-23
A	EP 0 520 336 A (FUJIREBIO KK) 30 December 1992 (1992-12-30) cited in the application claim 1 ---	1-23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 September 1999	12/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

2

International Application No
PCT/EP 99/02620

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DE 196 42 591 A (BASF AG) 16 April 1998 (1998-04-16) claim 1 ---	1-23
P,Y	WO 98 25883 A (BASF AG ;MOELLER ACHIM (DE); LUBISCH WILFRIED (DE); TREIBER HANS J) 18 June 1998 (1998-06-18) claim 1 ---	1-23
P,Y	WO 98 23581 A (BASF AG ;MOELLER ACHIM (DE); LUBISCH WILFRIED (DE); TREIBER HANS J) 4 June 1998 (1998-06-04) claim 1 ---	1-23
P,Y	WO 98 25899 A (BASF AG ;MOELLER ACHIM (DE); LUBISCH WILFRIED (DE); TREIBER HANS J) 18 June 1998 (1998-06-18) claim 1 -----	1-23

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

b. .mation on patent family members

Interna' .l Application No
PCT/EP 99/02620

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0611756	A	24-08-1994	AU	5496494	A	25-08-1994
			CA	2115913	A	20-08-1994
			CN	1107363	A	30-08-1995
			FI	940788	A	20-08-1994
			HU	66219	A	28-10-1994
			JP	2848232	B	20-01-1999
			JP	7101924	A	18-04-1995
			JP	9208545	A	12-08-1997
			NO	940550	A	22-08-1994
			NZ	250905	A	24-03-1997
			US	5498728	A	12-03-1996
			US	5716980	A	10-02-1998
			US	5639781	A	17-06-1997
WO 9212140	A	23-07-1992	AU	654834	B	24-11-1994
			AU	9155391	A	17-08-1992
			CA	2098702	A	29-06-1992
			EP	0564561	A	13-10-1993
			JP	6504547	T	26-05-1994
			US	5257901	A	02-11-1993
WO 9639194	A	12-12-1996	US	5783434	A	21-07-1998
			US	5849711	A	15-12-1998
			CA	2221684	A	12-12-1996
			EP	0831920	A	01-04-1998
			US	5858982	A	12-01-1999
EP 0520336	A	30-12-1992	JP	5163221	A	29-06-1993
			CA	2071621	A,C	20-12-1992
			JP	2697495	B	14-01-1998
			JP	6287167	A	11-10-1994
			KR	9511406	B	04-10-1995
			JP	5345753	A	27-12-1993
DE 19642591	A	16-04-1998	AU	4777097	A	11-05-1998
			WO	9816512	A	23-04-1998
			EP	0934273	A	11-08-1999
			HR	970549	A	31-08-1998
			NO	991761	A	14-04-1999
WO 9825883	A	18-06-1998	AU	5752398	A	03-07-1998
			HR	970680	A	31-10-1998
			NO	992821	A	11-06-1999
WO 9823581	A	04-06-1998	DE	19648793	A	28-05-1998
			AU	5481498	A	22-06-1998
			HR	970637	A	31-10-1998
			NO	992492	A	25-05-1999
WO 9825899	A	18-06-1998	DE	19650975	A	10-06-1998
			AU	5558098	A	03-07-1998
			HR	970671	A	31-10-1998
			NO	992770	A	08-06-1999

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 99/02620

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPK 6 C07D295/12 A61K31/50 C07D403/04 C07D317/58 C07D207/06
C07D215/06 C07D215/24 C07D217/04 C07D213/70 C07D213/30
C07C237/32 C07C311/08 C07C311/21

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 C07D C07C A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	EP 0 611 756 A (TAKEDA CHEMICAL INDUSTRIES LTD) 24. August 1994 (1994-08-24) siehe Anspruch 1, S.6(Z.38-54) und S.51(Ex.178). ---	1-23
Y	WO 92 12140 A (GEORGIA TECH RES INST) 23. Juli 1992 (1992-07-23) in der Anmeldung erwähnt Ansprüche 5,10,16 ---	1-23
Y	WO 96 39194 A (ATHENA NEUROSCIENCES INC) 12. Dezember 1996 (1996-12-12) Anspruch 1; Beispiel 71 ---	1-23
A	EP 0 520 336 A (FUJIREBIO KK) 30. Dezember 1992 (1992-12-30) in der Anmeldung erwähnt Anspruch 1 --- -/--	1-23

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist

"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
9. September 1999	12/10/1999

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

2

Internationales Aktenzeichen
PCT/EP 99/02620

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	DE 196 42 591 A (BASF AG) 16. April 1998 (1998-04-16) Anspruch 1	1-23
P,Y	WO 98 25883 A (BASF AG ;MOELLER ACHIM (DE); LUBISCH WILFRIED (DE); TREIBER HANS J) 18. Juni 1998 (1998-06-18) Anspruch 1	1-23
P,Y	WO 98 23581 A (BASF AG ;MOELLER ACHIM (DE); LUBISCH WILFRIED (DE); TREIBER HANS J) 4. Juni 1998 (1998-06-04) Anspruch 1	1-23
P,Y	WO 98 25899 A (BASF AG ;MOELLER ACHIM (DE); LUBISCH WILFRIED (DE); TREIBER HANS J) 18. Juni 1998 (1998-06-18) Anspruch 1	1-23

2

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/EP 99/02620

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP 0611756 A	24-08-1994	AU 5496494 A	25-08-1994
		CA 2115913 A	20-08-1994
		CN 1107363 A	30-08-1995
		FI 940788 A	20-08-1994
		HU 66219 A	28-10-1994
		JP 2848232 B	20-01-1999
		JP 7101924 A	18-04-1995
		JP 9208545 A	12-08-1997
		NO 940550 A	22-08-1994
		NZ 250905 A	24-03-1997
		US 5498728 A	12-03-1996
		US 5716980 A	10-02-1998
		US 5639781 A	17-06-1997
WO 9212140 A	23-07-1992	AU 654834 B	24-11-1994
		AU 9155391 A	17-08-1992
		CA 2098702 A	29-06-1992
		EP 0564561 A	13-10-1993
		JP 6504547 T	26-05-1994
		US 5257901 A	02-11-1993
WO 9639194 A	12-12-1996	US 5783434 A	21-07-1998
		US 5849711 A	15-12-1998
		CA 2221684 A	12-12-1996
		EP 0831920 A	01-04-1998
		US 5858982 A	12-01-1999
EP 0520336 A	30-12-1992	JP 5163221 A	29-06-1993
		CA 2071621 A,C	20-12-1992
		JP 2697495 B	14-01-1998
		JP 6287167 A	11-10-1994
		KR 9511406 B	04-10-1995
		JP 5345753 A	27-12-1993
DE 19642591 A	16-04-1998	AU 4777097 A	11-05-1998
		WO 9816512 A	23-04-1998
		EP 0934273 A	11-08-1999
		HR 970549 A	31-08-1998
		NO 991761 A	14-04-1999
WO 9825883 A	18-06-1998	AU 5752398 A	03-07-1998
		HR 970680 A	31-10-1998
		NO 992821 A	11-06-1999
WO 9823581 A	04-06-1998	DE 19648793 A	28-05-1998
		AU 5481498 A	22-06-1998
		HR 970637 A	31-10-1998
		NO 992492 A	25-05-1999
WO 9825899 A	18-06-1998	DE 19650975 A	10-06-1998
		AU 5558098 A	03-07-1998
		HR 970671 A	31-10-1998
		NO 992770 A	08-06-1999

OPIC
OFFICE DE LA PROPRIÉTÉ INTELLECTUELLE DU CANADA

CIPO
CANADIAN INTELLECTUAL PROPERTY OFFICE

(12) (19) (CA) **Demande-Application**

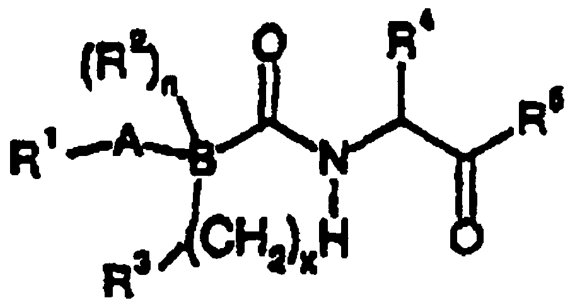
(21) (A1) **2,328,720**
(86) 1999/04/19
(87) 1999/10/28

(72) LUBISCH, WILFRIED, DE
(72) MOLLER, ACHIM, DE
(72) TREIBER, HANS-JORG, DE
(72) KNOPP, MONIKA, DE
(71) BASF AKTIENGESELLSCHAFT, DE

(51) Int.Cl.^{6} C07D 295/12, C07D 213/70, C07D 317/58, A61K 31/50, C07C 237/32, C07D 213/30, C07D 215/24, C07C 311/21, C07C 311/08, C07D 215/06, C07D 207/06, C07D 403/04, C07D 217/04
(30) 1998/04/20 (198 17 460.8) DE

(54) **NOUVEAUX AMIDES HETEROCYCLIQUEMENT SUBSTITUES A ACTION DE PROTEASES DE CYSTEINE**

(54) **NOVEL HETEROCYCLICALLY SUBSTITUTED AMIDES WITH CYSTEINE PROTEASE-INHIBITING EFFECT**



(I)

(57) L'invention concerne des amides de la formule générale (I), qui sont des inhibiteurs d'enzymes, notamment de protéases de cystéine.

(57) The invention relates to amides of the general formula (I), which are inhibitors of enzymes, especially cysteine proteases.

110

CA 02328720 2000-10-13

PCT
WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro

INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 : C07D 295/12, A61K 31/50, C07D 403/04, 317/58, 207/06, 215/06, 215/24, 217/04, 213/70, 213/30, C07C 237/32, 311/08, 311/21

A1

(11) Internationale Veröffentlichungsnummer: WO 99/54320

(43) Internationales Veröffentlichungsdatum: 28. Oktober 1999 (28.10.99)

(21) Internationales Aktenzeichen: PCT/EP99/02620

(22) Internationales Anmeldedatum: 19. April 1999 (19.04.99)

(30) Prioritätsdaten:
198 17 460.8 20. April 1998 (20.04.98) DE

(71) Anmelder (*für alle Bestimmungsstaaten ausser US*): BASF AKTIENGESELLSCHAFT [DE/DE]; D-67056 Ludwigshafen (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder (*nur für US*): LUBISCH, Wilfried [DE/DE]; Häusererstrasse 15, D-69115 Heidelberg (DE). MÖLLER, Achim [DE/DE]; Im Zaunrücken 10, D-67269 Grünstadt (DE). TREIBER, Hans-Jörg [DE/DE]; Sperberweg 1, D-68782 Brühl (DE). KNOPP, Monika [DE/DE]; Karl-Dillinger-Strasse 19, D-67071 Ludwigshafen (DE).

(74) Gemeinsamer Vertreter: BASF AKTIENGESELLSCHAFT; D-67056 Ludwigshafen (DE).

(81) Bestimmungsstaaten: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, ZA, eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

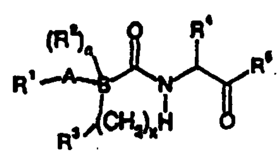
Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.

48969

020602

(54) Title: NOVEL HETEROCYCLICALLY SUBSTITUTED AMIDES WITH CYSTEINE PROTEASE-INHIBITING EFFECT

(54) Bezeichnung: NEUE HETEROCYCLISCH SUBSTITUIERTE AMIDE MIT CYSTEIN-PROTEASE HEMMENDER WIRKUNG



(I)

(57) Abstract

The invention relates to amides of the general formula (I), which are inhibitors of enzymes, especially cysteine proteases.

(57) Zusammenfassung

Die Erfindung betrifft Amide der allgemeinen Formel (I), die Inhibitoren von Enzymen, insbesondere Cystein-Proteasen darstellen.

NOVEL HETEROCYCLICALLY SUBSTITUTED AMIDES WITH CYSTEINE PROTEASE-INHIBITING EFFECT

The present invention relates to novel amides which are inhibitors of enzymes, especially cysteine proteases such as calpain (= calcium dependant cysteine proteases) and its isoenzymes and cathepsins, for example B and L.

Calpains are intracellular proteolytic enzymes from the group of cysteine proteases and are found in many cells. Calpains are activated by an increase in the calcium concentration, a distinction being made between calpain I or μ-calpain, which is activated by μ-molar concentrations of calcium ions, and calpain II or m-calpain, which is activated by m-molar concentrations of calcium ions (P. Johnson, Int. J. Biochem. 1990, 22(8), 811-22). Further calpain isoenzymes have now been postulated too (K. Suzuki et al., Biol. Chem. Hoppe-Seyler, 1995, 376(9), 523-9).

It is suspected that calpains play an important part in various physiological processes. These include cleavages of regulatory proteins such as protein kinase C, cytoskeletal proteins such as MAP 2 and spectrin, muscle proteins, protein degradation in rheumatoid arthritis, proteins in the activation of platelets, neuropeptide metabolism, proteins in mitosis and others which are listed in M.J. Barrett et al., Life Sci. 1991, 48, 1659-69 and K.K. Wang et al., Trends in Pharmacol. Sci., 1994, 15, 412-9.

Elevated calpain levels have been measured in various pathophysiological processes, for example: ischemia of the heart (e.g. myocardial infarct), of the kidney or of the central nervous system (e.g. stroke), inflammations, muscular dystrophies, cataracts of the eyes, injuries to the central nervous system (e.g. trauma), Alzheimer's disease etc. (see K.K. Wang,

above). It is suspected that there is a connection between these disorders and elevated and persistent intracellular calcium levels. This results in overactivation of calcium-dependent processes, which are then no longer subject to physiological control. Accordingly, overactivation of calpains may also induce pathophysiological processes.

It has therefore been postulated that inhibitors of calpain enzymes may be useful for treating these disorders. Various investigations have confirmed this. Thus, Seung-Chyul Hong et al., Stroke 1994, 25(3), 663-9 and R.T. Bartus et al., Neurological Res. 1995, 17, 249-58 have shown a neuroprotective effect of calpain inhibitors in acute neurodegenerative disorders or ischemias like those occurring after a stroke. Likewise, calpain inhibitors improved the recovery of the memory deficits and neuromotor disturbances occurring after experimental brain trauma (K.E. Saatman et al. Proc. Natl. Acad. Sci. USA, 1996, 93, 3428-3433). C.L. Edelstein et al., Proc. Natl. Acad. Sci. USA, 1995, 92, 7662-6, found a protective effect of calpain inhibitors on kidneys damaged by hypoxia. Yoshida, Ken Ischi et al., Jap. Circ. J. 1995, 59(1), 40-8, were able to show beneficial effects of calpain inhibitors after cardiac damage produced by ischemia or reperfusion. Since the release of the β-AP4 protein is inhibited by calpain inhibitors, a potential therapeutic use for Alzheimer's disease has been proposed (J. Higaki et al., Neuron, 1995, 14, 651-59). The release of interleukin-1α is likewise inhibited by calpain inhibitors (N. Watanabe et al., Cytokine 1994, 6(6), 597-601). It has further been found that calpain inhibitors have cytotoxic effects on tumor cells (E. Shiba et al. 20th Meeting Int. Ass. Breast Cancer Res., Sendai Jp, 1994, 25-28 Sept., Int. J. Oncol. 5 (Suppl.), 1994, 381).

Further possible uses of calpain inhibitors are detailed in K.K. Wang, Trends in Pharmacol. Sci., 1994, 15, 412-8.

Calpain inhibitors have already been described in the literature. However, these are predominantly either irreversible or peptide inhibitors. Irreversible inhibitors are usually alkylating substances and have the disadvantage that they react nonselectively or are unstable in the body. Thus, these inhibitors often show unwanted side effects such as toxicity, and are accordingly of limited use or unusable. The irreversible inhibitors can be said to include, for example, the epoxides E 64 (E.B. McGowan et al., Biochem. Biophys. Res. Commun. 1989, 158, 432-5), α-halo ketones (H. Angliker et al., J. Med. Chem. 1992, 35, 216-20) or disulfides (R. Matsueda et al., Chem. Lett. 1990, 191-194).

Many known reversible inhibitors of cysteine proteases such as calpain are peptide aldehydes, in particular dipeptide and tripepide [sic] aldehydes such as, for example, Z-Val-Phe-H (MDL 28170) (S. Mehdi, Tends [sic] in Biol. Sci. 1991, 16, 150-3). Under physiological conditions, peptide aldehydes have the disadvantage that, owing to the high reactivity, they are often unstable, may be rapidly metabolized and are prone to nonspecific reactions which may cause toxic effects (J.A. Fehrentz and B. Castro, Synthesis 1983, 676-78. JP 08183771 (CA 1996, 605307) and EP 520336 have described aldehydes derived from 4-piperidinoylamides [sic] and 1-carbonylpiperidino-4-ylamides [sic] as calpain inhibitors. However, the aldehydes which are claimed herein and are derived from amides of the general structure I with heteroaromatic substituents have not previously been described.

Peptide ketone derivatives are likewise inhibitors of cysteine proteases, in particular calpains. Thus, for

example, ketone derivatives where the keto group is activated by an electron-attracting group such as CF_3 are known to be inhibitors of serine proteases. In the case of cysteine proteases, derivatives with ketones activated by CF_3 or similar groups have little or no activity (M.R. Angelastro et al., J. Med. Chem. 1990, 33, 11-13). Surprisingly, to date only ketone derivatives in which, on the one hand, leaving groups in the α position cause irreversible inhibition and, on the other hand, the keto group is activated by a carboxylic acid derivative have been found to be effective inhibitors of calpain (see M.R. Angelastro et al., see above; WO 92/11850; WO 92,12140; WO 94/00095 and WO 95/00535). However, only peptide derivatives of these keto amides and keto esters have been described as effective (Zhaozhao Li et al., J. Med. Chem. 1993, 36, 3472-80; S.L. Harbenson et al., J. Med. Chem. 1994, 37, 2918-29 and see above M.R. Angelastro et al.).

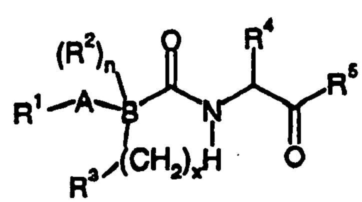
Ketobenzamides have already been described in the literature. Thus, the keto ester $PhCO\text{-}Abu\text{-}COOCH_2CH_3$ has been described in WO 91/09801, WO 94/00095 and 92/11850. The analogous phenyl derivative $Ph\text{-}CONH\text{-}CH(CH_2Ph)\text{-}CO\text{-}COCOOCH_3$ was, however, found to be only a weak calpain inhibitor in M.R. Angelastro et al., J. Med. Chem. 1990, 33, 11-13. This derivative is also described in J.P. Burkhardt, Tetrahedron Lett., 1988, 3433-36. The significance of the substituted benzamides has, however, never been investigated to date.

In a number of therapies, such as [lacuna] stroke, the active ingredients are administered intravenously, for example as infusion solution. To do this it is necessary to have available substances, in this case calpain inhibitors, which have adequate solubility in water so that an infusion solution can be prepared. Many of the described calpain inhibitors have, however, the disadvantage that they have only low or no

solubility in water and thus are unsuitable for intravenous administration. Active ingredients of this type can be administered only with ancillary substances intended to confer solubility in water (cf. R.T. Bartus et al. J. Cereb. Blood Flow Metab. 1994, 14, 537-544). These ancillary substances, for example polyethylene glycol, often have side effects, however, or are even incompatible. A non-peptide calpain inhibitor which is soluble in water without ancillary substances would thus be a great advantage. No such inhibitor has been described to date, and it would thus be novel.

Substituted non-peptide aldehydes, keto carboxylic esters and keto amide derivatives were described in the present invention. These compounds are novel and surprisingly show the possibility of obtaining potent non-peptide inhibitors of cysteine proteases, such as, for example, calpain, by incorporating rigid structural fragments. In addition, all the present compounds of the general formula I have at least one aliphatic amine radical and are thus able to bind [sic] salts with acids. A large number of these substances are soluble in water in a 0.5% strength solution at pH 0.4-5 and thus the show the required profile for intravenous administration as is necessary, for example, for stroke therapy.

The present invention relates to amides of the general formula I



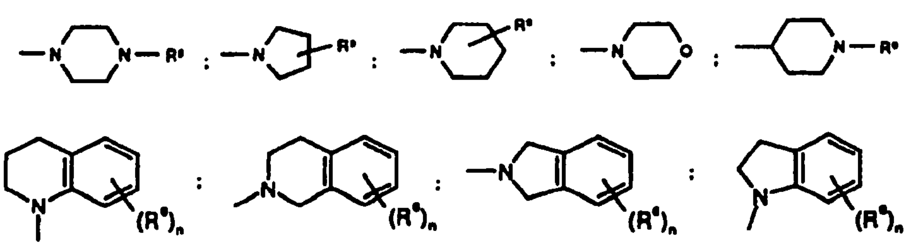
and their tautomeric and isomeric forms, possible enantiomeric and diastereomeric forms, and possible physiologically tolerated salts, in which the variables

have the following meanings:

R^1 can be hydrogen, C_1-C_6-alkyl, branched and unbranched, phenyl, naphthyl, quinolyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, quinazolyl, quinoxalyl, thienyl, benzothienyl, benzofuranyl, furanyl and indolyl, it being possible for the rings also to be substituted by up to 3 R^6 radicals, and

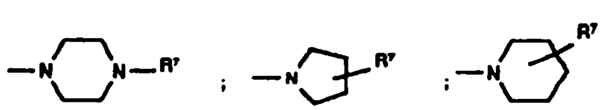
R^2 are hydrogen, C_1-C_6-alkyl, branched or unbranched, O-C_1-C_6-alkyl, branched or unbranched, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyl-phenyl, C_2-C_6-alkenyl-phenyl, C_2-C_6-alkynyl-phenyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, NHCO-C_1-C_4-alkyl, NHCO-phenyl, $CONHR^9$, $NHSO_2$-C_1-C_4-alkyl, $NHSO_2$-phenyl, SO_2-C_1-C_4-alkyl and SO_2-phenyl, and

R^3 can be NR^7R^8 or a ring such as



R^4 is -C_1-C_6-alkyl, branched or unbranched, which may also carry a phenyl, pyridyl or naphthyl ring which is in turn substituted by a maximum of two R^6 radicals, and

R^5 is hydrogen, $COOR^{11}$ and CO-Z in which Z is $NR^{12}R^{13}$ and

 and

R^6 is hydrogen, C_1-C_4-alkyl, branched or unbranched, -O-C_1-C_4-alkyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, -NHCO-C_1-C_4-alkyl, -NHCO-phenyl, -$NHSO_2$-C_1-C_4-alkyl, -$NHSO_2$-phenyl, -SO_2-C_1-C_4-alkyl and -SO_2-phenyl, and

R^7 is hydrogen, C_1-C_6-alkyl, linear or branched, and which may be substituted by a phenyl ring which itself may also be substituted by one or two R^{10} radicals, and

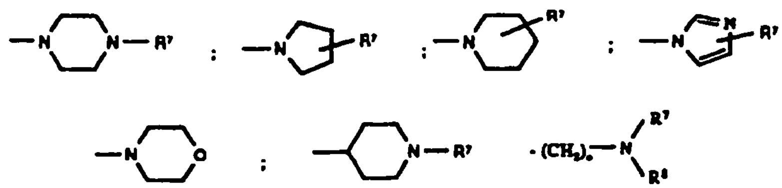
R^8 is hydrogen, C_1-C_6-alkyl, linear or branched, which may be substituted by a phenyl ring which may itself also be substituted by one or two R^{10} radicals, and

R^9 is hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a substituent R^{16}, or phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, naphthyl, quinolyl, imidazolyl, which may also carry one or two substituents R^{14}, and

R^{10} can be hydrogen, C_1-C_4-alkyl, branched or unbranched, -O-C_1-C_4-alkyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, -NHCO-C_1-C_4-alkyl, -NHCO-phenyl, -$NHSO_2$-C_1-C_4-alkyl, -$NHSO_2$-phenyl, -SO_2-C_1-C_4-alkyl and -SO_2-phenyl

R^{11} is hydrogen, C_1-C_6-alkyl, linear or branched, and which may be substituted by a phenyl ring which may itself also be substituted by one or two R^{10} radicals, and

R^{12} is hydrogen, C_1-C_6-alkyl, branched and unbranched, and



[sic]

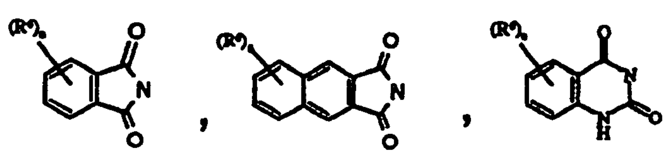
R^{13} is hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also be substituted by a phenyl ring which may also carry an R^{10} radical, and by [lacuna]
and

R^{14} is hydrogen, C_1-C_6-alkyl, branched or unbranched, O-C_1-C_6-alkyl, branched or unbranched, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, or two R^{14} radicals may represent a bridge $OC(R^{15})_2O$, and

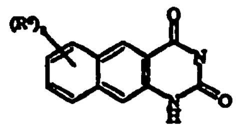
R^{15} is hydrogen, C_1-C_6-alkyl, branched and unbranched, and

R^{16} can be a phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, pyrrolyl, naphthyl, quinolyl, imidazolyl ring, which may also carry one or two substituents R^6, and

A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-(CH_2)_o-SO-(CH_2)_m-$, $-(CH_2)_o-SO_2-(CH_2)_m-$, $-CH=CH-$, $-C{\equiv}C-$, $-CO-CH=CH-$, $-(CH_2)_o-CO-(CH_2)_m-$, $-(CH_2)_m-NHCO-(CH_2)_o-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-NHSO_2-(CH_2)_o-$, $-NH-CO-CH=CH-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$, $-CH=CH-CONH-$ and



and



[sic]

R^1-A together are also
[lacuna]
and

B is phenyl, pyridine, pyrimidine, pyrazine, imidazole and thiazole and

x is 1, 2 or 3, and

n is a number 0, 1 or 2, and

m, o is, independently of one another, a number 0, 1, 2, 3 or 4.

The compounds of the formula I can be employed as racemates, as enantiomerically pure compounds or as diastereomers. If enantiomerically pure compounds are required, these can be obtained, for example, by carrying out a classical racemate resolution with the compounds of the formula I or their intermediates using a suitable optically active base or acid. On the other hand, the enantiomeric compounds can likewise be prepared by using commercially purchasable compounds, for example optically active amino acids such as phenylalanine, tryptophan and tyrosine.

The invention also relates to compounds which are mesomers or tautomers of compounds of the formula I, for example those in which the aldehyde or keto group in formula I is in the form of an enol tautomer.

The invention further relates to the physiologically tolerated salts of the compounds I which can be obtained by reacting compounds I with a suitable acid

or base. Suitable acids and bases are listed, for example, in Fortschritte der Arzneimittelforschung, 1966, Birkhäuser Verlag, Vol. 10, pp. 224-285. These include, for example, hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid etc., and sodium hydroxide, lithium hydroxide, potassium hydroxide and tris.
The amides I according to the invention can be prepared in various ways which has [sic] been outlined in the synthesis scheme.

Synthesis scheme

Heterocyclic carboxylic acids II are linked to suitable amino alcohols III to give the corresponding amides IV. Conventional peptide coupling methods are used for this, as detailed either in C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, page 972 et seq., or in Houben-Weyl, Methoden der organischen Chemie, 4th edition, E5, Chapter V. It is preferred to use "activated" acid derivatives of II, with the acid group COOH being converted into a group COL. L is a leaving group such as, for example, Cl, imidazole and N-hydroxybenzotriazole. This activated acid is then reacted with amines to give the amides IV. The reaction takes place in anhydrous inert solvents such as methylene chloride, tetrahydrofuran and dimethylformamide at temperatures from -20 to +25°C.

These alcohol derivatives IV can be oxidized to the aldehyde derivatives I according to the invention. Various conventional oxidation reactions can be used for this (see C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, page 604 et seq.) such as, for example, Swern and Swern-analogous oxidations (T.T. Tidwell, Synthesis, 1990, 857-70), sodium hypochloride [sic]/TEMPO (S.L. Harbenson et al., see above) or Dess-Martin (J. Org. Chem. 1983, 48, 4155). Preferably used for this are inert aprotic

solvents such as dimethylformamide, tetrahydrofuran or methylene chloride with oxidizing agents such as DMSO/py x SO_3 or DMSO/oxalyl chloride at temperatures from -50 to +25°C, depending on the method (see above literature).

Alternatively, the carboxylic acid II can be reacted with amino hydroxamic acid derivatives VI to give benzamides VII. The reaction in this case is carried out in the same way as for preparing IV. The hydroxamic derivatives VI can be obtained from the protected amino acids V by reaction with a hydroxylamine. An amide preparation process already described is also used in this case. Elimination of the protective group X, for example Boc, takes place in a normal way, for example with trifluoroacetic acid. The amide hydroxamic acids VII obtained in this way can be converted by reduction into the aldehydes I according to the invention. The reducing agent used for this is, for example, lithium aluminum hydride at temperatures from -60 to 0°C in inert solvents such as tetrahydrofuran or ether.

Carboxylic acids or acid derivatives such as esters IX (P = COOR', COSR') can also be prepared in analogy to the last process and can likewise be converted by reduction into the aldehydes I according to the invention. These processes are listed in R.C. Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, pages 619-26.

The amides I according to the invention, which have heterocyclic substituents and have a keto amide or keto ester group, can be prepared in various ways which have been outlined in synthesis schemes 2 and 3.

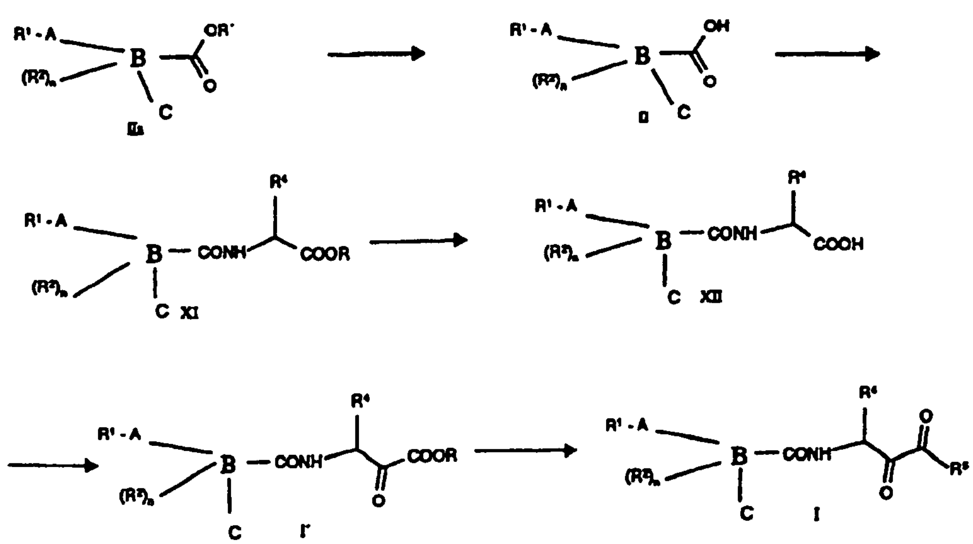
The carboxylic esters IIa are converted, where appropriate, with acids or bases such as lithium hydroxide, sodium hydroxide or potassium hydroxide in aqueous medium or in mixtures of water and organic

solvents such as alcohols or tetrahydrofuran at room temperature or elevated temperatures, such as 25-100°C, into the acids II.

These acids II are linked to an α-amino acid derivative using customary conditions which are listed, for example, in Houben-Weyl, Methoden der organischen Chemie, 4th edition, E5, Chapter V, and C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, Ch. 9.

For example, the carboxylic acids II are converted into the "activated" acid derivatives IIb = Y-COL, where L is a leaving group such as Cl, imidazole and N-hydroxybenzotriazole, and then converted into the derivative XI by adding an amino acid derivative $H_2N-CH(R^3)-COOR$. This reaction takes place in anhydrous inert solvents such as methylene chloride, tetrahydrofuran and dimethylformamide at temperatures from -20 to +25°C.

Scheme 1

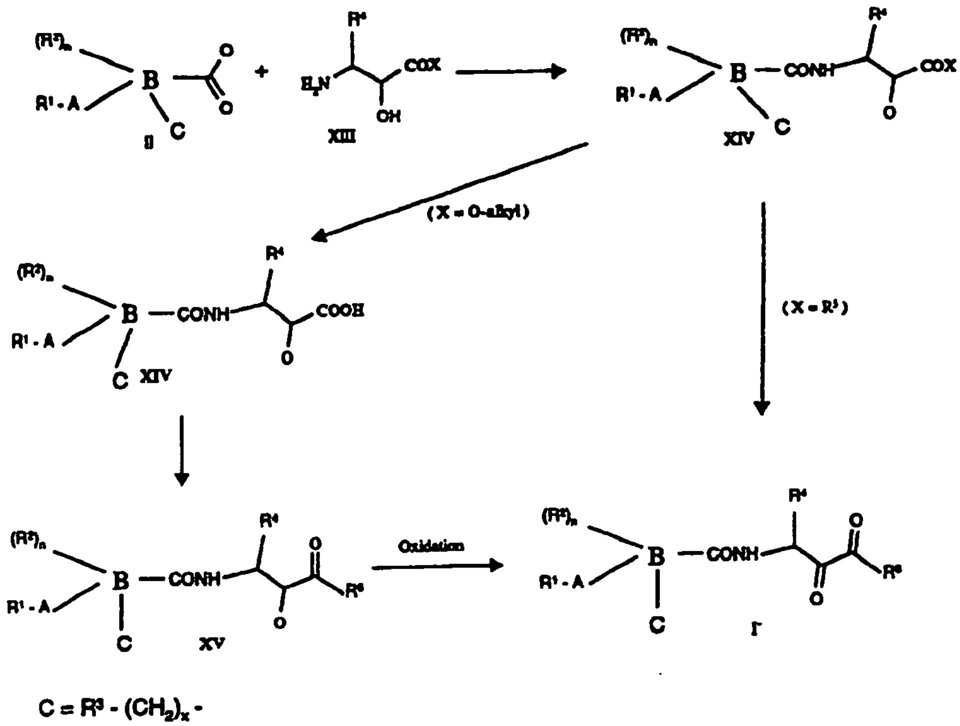


$C = R^3-(CH_2)_x-$

The derivatives XI, which are usually esters, are converted into the keto carboxylic acids XII by hydrolysis analogous to that described above. The keto esters I' are prepared in a Dakin-West-analogous reaction using a method of ZhaoZhao Li et al., J. Med. Chem., 1993, 36, 3472-80. This entails a [sic] carboxylic acids such as XII being reacted with oxalic monoester chloride at elevated temperature (50-100°C) in solvents such as, for example, tetrahydrofuran, and the product obtained in this way then being reacted with bases such as sodium ethanolate in ethanol at temperatures of 25-80°C to give the keto ester I' according to the invention. The keto esters I' can be hydrolyzed as described above for example to keto carboxylic acids according to the invention.

The reaction to give keto benzamides I' likewise takes place in analogy to the method of ZhaoZhao Li et al. (see above). The keto group in I' is protected by adding 1,2-ethanedithiol with Lewis acid catalysis, such as, for example, boron trifluoride etherate, in inert solvents such as methylene chloride at room temperature, resulting in a dithiane. These derivatives are reacted with amines R^3-H in polar solvents such as alcohols at temperatures of 0-80°C, resulting in the keto amides I (R^4 = Z or NR^7R^8).

Scheme 2



An alternative method is depicted in scheme 2. The keto carboxylic acids II are reacted with amino hydroxy carboxylic acid derivatives XIII (for preparation of XIII, see S.L. Harbenson et al., J. Med. Chem. 1994, 37, 2918-29 or J.P. Burkhardt et al. Tetrahedron Lett. 1988, 29, 3433-3436) using customary peptide coupling methods (see above, Houben-Weyl), resulting in amides XIV. These alcohol derivatives XIV can be oxidized to the keto carboxylic acid derivatives I according to the invention. It is possible to use for this various customary oxidation reactions (see C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, [lacuna] page 604 et seq.) such as, for example, Swern and Swern-analogous oxidations, preferably dimethyl sulfoxide/pyridine-sulfur trioxide complex in solvents such as methylene chloride or tetrahydrofuran, where appropriate with the addition of dimethyl sulfoxide, at room temperature or temperatures from -50 to 25°C (T.T. Tidwell, Synthesis 1990, 857-70) or sodium

hypochloride [sic]/TEMPO (S.L. Harbenson et al., see above).

In the case of α-hydroxy esters XIV (X = O-alkyl), these can be hydrolyzed to carboxylic acids XV using methods analogous to those above, but preferably using lithium hydroxide in water/tetrahydrofuran mixtures at room temperature. Other esters or amides XVI are prepared by reaction with alcohols or amines under coupling conditions described above. The alcohol derivative XVI can be oxidized to give keto carboxylic acid derivatives I according to the invention.

The preparation of the carboxylic esters II had already been described for some instances, or it takes place by usual chemical methods.

Compounds in which X is a bond are prepared by conventional aromatic coupling, for example Suzuki coupling with boric acid derivatives and halides with palladium catalysis or copper-catalyzed coupling of aromatic halides. The alkyl-bridged radicals ($X = -(CH_2)_m-$) can be prepared by reducing the analogous ketones or by alkylating the organolithium, e.g. ortho-phenyloxazolidines, or other organometallic compounds (cf. I.M. Dordor et al., J. Chem. Soc. Perkins Trans. I, 1984, 1247-52).

Ether-bridged derivatives are prepared by alkylating the corresponding alcohols or phenols with halides.

The sulfoxides and sulfones can be obtained by oxidizing the corresponding thioethers.

Alkene- and alkyne-bridged compounds are prepared, for example, by the Heck reaction from aromatic halides and corresponding alkenes and alkynes (cf. I. Sakamoto et al., Chem. Pharm. Bull., 1986, 34, 2754-59).

The chalcones are produced by condensing acetophenones with aldehydes and can, where appropriate, be converted into the analogous alkyl derivatives by hydrogenation.

Amides and sulfonamides are prepared from the amines and acid derivatives in analogy to the methods described above.

The dialkylaminoalkyl substituents are obtained by reductive amination of the aldehyde derivatives with the appropriate amines in the presence of boron hydrides such as the BH_3/pyridine complex or or [sic] $NaBH_3CN$ (A.F. Abdel-Magid, C.A. Maryanoff, K.G. Carson, Tetrahedron Lett. 10990 [sic], 31, 5595; A.E. Moormann, Synth. Commun. 1993, 23, 789).

The amides I with heterocyclic substituents of the present invention are inhibitors of cysteine proteases, especially cysteine proteases such as calpains I and II and cathepsins B and L.

The inhibitory effect of the amides I with heterocyclic substituents has been determined using enzyme assays known from the literature, determining as criterion of effect a concentration of the inhibitor at which 50% of the enzyme activity is inhibited (= IC_{50}). The amides I were measured in this way for their inhibitory effect on calpain I, calpain II and cathepsin B.

Cathepsin B assay

The inhibition of cathepsin B was determined by a method analogous to that of S. Hasnain et al., J. Biol. Chem., 1993, 268, 235-40.

2 µl of an inhibitor solution prepared from inhibitor and DMSO (final concentrations: 100 µM to 0.01 µM) are added to 88 µl of cathepsin B (cathepsin B from human liver (Calbiochem), diluted to 5 units in 500 µM

buffer). This mixture is preincubated at room temperature (25°C) for 60 minutes and then the reaction is started by adding 10 µl of 10 mM Z-Arg-Arg-pNA (in buffer with 10% DMSO). The reaction is followed in a microtiter plate reader at 405 nM [sic] for 30 minutes. The IC_{50}s are then determined from the maximum gradients.

Calpain I and II assay

The testing of the inhibitory properties of calpain inhibitors takes place in buffer with 50 mM tris-HCl, pH 7.5; 0.1 M NaCl; 1 mM dithiotreithol [sic]; 0.11 mM $CaCl_2$, using the fluorogenic calpain substrate Suc-Leu-Tyr-AMC (25 mM dissolved in DMSO, Bachem/ Switzerland). Human µ-calpain is isolated from erythrocytes, and enzyme with a purity > 95%, assessed by SDS-PAGE, Western blot analysis and N-terminal sequencing, is obtained after several chromatographic steps (DEAE-Sepharose, phenyl-Sepharose, Superdex 200 and blue Sepharose). The fluorescence of the cleavage product 7-amino-4-methylcoumarin (AMC) is followed in a Spex Fluorolog fluorimeter at λex = 380 nm and λem = 460 nm. The cleavage of the substrate is linear in a measurement range of 60 min., and the autocatalytic activity of calpain is low, if the tests are carried out at temperatures of 12°C. The inhibitors and the calpain substrate are added to the test mixture as DMSO solutions, and the final concentration of DMSO ought not to exceed 2%.

In a test mixture, 10 µl of substrate (250 µM final) and then 10 µl of µ-calpain (2 µg/ml final, i.e. 18 nM) are added to a 1 ml cuvette containing buffer. The calpain-mediated cleavage of the substrate is measured for 15 - 20 min. Then 10 µl of inhibitor (50-100 µM solution in DMSO) are added and the inhibition of cleavage is measured for a further 40 min.

K_i values are determined using the classical equation for reversible inhibition:
(Methods in Enzymology,)

Ki = I(v0/vi)-1; where I = inhibitor concentration, v0 = initial rate before addition of the inhibitor; vi = reaction rate at equilibrium.

The rate is calculated from v = AMC liberation/time, i.e. height/time.

Calpain is an intracellular cysteine protease. Calpain inhibitors must pass through the cell membrane in order to prevent intracellular proteins from being broken down by calpain. Some known calpain inhibitors, such as, for example, E 64 and leupeptin, cross cell membranes only poorly and accordingly show only a poor effect on cells, although they are good calpain inhibitors. The aim is to find compounds better able to cross membranes. Human platelets are used to demonstrate the ability of calpain inhibitors to cross membranes.

Calpain-mediated breakdown of tyrosine kinase pp60src in platelets

Tyrosine kinase pp60src is cleaved by calpain after activation of platelets. This has been investigated in detail by Oda et al. in J. Biol. Chem., 1993, Vol. 268, 12603-12608. This revealed that the cleavage of pp60src can be prevented by calpeptin, a calpain inhibitor. The cellular efficacy of our substances was tested based on this publication. Fresh, citrated, human blood was centrifuged at 200 g for 15 min. The platelet-rich plasma was pooled and diluted 1:1 with platelet buffer (platelet buffer: 68 mM NaCl, 2.7 mM KCl, 0.5 mM $MgCl_2 \times 6 H_2O$, 0.24 mM $NaH_2PO_4 \times H_2O$, 12 mM $NaHCO_3$, 5.6 mM glucose, 1 mM EDTA, pH 7.4). After a centrifugation step and washing step with platelet

buffer, the platelets were adjusted to 10^7 cells/ml. The human platelets were isolated at RT.

In the assay mixture, isolated platelets (2×10^6) were preincubated with various concentrations of inhibitors (dissolved in DMSO) at 37°C for 5 min. The platelets were then activated with 1 µM ionophore A23187 and 5 mM $CaCl_2$. After incubation for 5 min., the platelets were briefly centrifuged at 13,000 rpm, and the pellet was taken up SDS sample buffer (SDS sample buffer: 20 mM Tris-HCl, 5 mM EDTA, 5 mM EGTA, 1 mM DTT, 0.5 mM PMSF, 5 µg/ml leupeptin, 10 µg/ml pepstatin, 10% glycerol and 1% SDS). The proteins were fractionated in a 12% gel, and pp60src and its 52 kDa and 47 kDa cleavage products were identified by Western blotting. The polyclonal rabbit antibody used, anti-cys-src ($pp60^{c\text{-}src}$), was purchased from Biomol Feinchemikalien (Hamburg). This primary antibody was detected using a second, HRP-coupled goat antibody (Boehringer Mannheim, FRG). The Western blotting was carried out by known methods.

The cleavage of pp60src was quantified by densitometry, using as controls unactivated (control 1: no cleavage) and ionophore- and calcium-treated platelets (control 2: corresponds to 100% cleavage). The ED_{50} corresponds to the concentration of inhibitor at which the intensity of the color reaction is reduced by 50%.

Glutamate-induced cell death in cortical neurones

The test was carried out as in Choi D.W., Maulucci-Gedde M.A. and Kriegstein A.R., "Glutamate neuro-toxicity in cortical cell culture". J. Neurosci. 1989, 7, 357-368.

The cortex halves were dissected out of 15-day old mouse embryos and the single cells were obtained enzymatically (trypsin). These cells (glia and cortical neurones) are seeded out in 24-well plates. After three

days (laminin-coated plates) or seven days (ornithine-coated plates), the mitosis treatment is carried out with FDU (5-fluoro-2-deoxyuridines [sic]). 15 days after preparation of the cells, cell death is induced by adding glutamate (15 minutes). After removal of glutamate, the calpain inhibitors are added. 24 hours later, the cell damage is estimated by determining lactate dehydrogenase (LDH) in the cell culture supernatant.

It is postulated that calpain is also involved in apoptotic cell death (M.K.T. Squier et al., J. Cell. Physiol. 1994, 159, 229-237; T. Patel et al. Faseb Journal 1996, 590, 587-597). For this reason, in another model, cell death was induced in a human cell line with calcium in the presence of a calcium ionophore. Calpain inhibitors must get inside the cell and inhibit calpain there in order to prevent the induced cell death.

Calcium-mediated cell death in NT2 cells

Cell death can be induced in the human cell line NT2 by calcium in the presence of the ionophore A 23187. 10^5 cells/well were plated out in microtiter plates 20 hours before the test. After this period, the cells were incubated with various concentrations of inhibitors in the presence of 2.5 µM ionophore and 5 mM calcium. 0.05 ml of XTT (Cell Proliferation Kit II, Boehringer Mannheim) was added to the reaction mixture after 5 hours. The optical density was determined approximately 17 hours later, in accordance with the manufacturer's information, in an SLT Easy Reader EAR 400. The optical density at which half the cells have died is calculated from the two controls with cells without inhibitors incubated in the absence and presence of ionophore.

Elevated glutamate activities occur in a number of neurological disorders of psychological disturbances and lead to states of overexcitation or toxic effects in the central nervous system (CNS). The effects of glutamate are mediated by various receptors. Two of these receptors are classified, in accordance with the specific agonists, as NMDA receptor and AMPA receptor. Antagonists to these glutamate-mediated effects can thus be employed for treating these disorders, in particular for therapeutic use for neurodegenerative disorders such as Huntington's chorea and Parkinson's disease, neurotoxic impairments after hypoxia, anoxia, ischemia and after lesions like those occurring after stroke and trauma, or else as antiepileptics (cf. Arzneim. Forschung 1990, 40, 511-514; TIPS, 1990, 11, 334-338; Drugs of the Future 1989, 14, 1059-1071). De [sic]

Protection from cerebral overexcitation by excitatory amino acids (NMDA and AMPA antagonism in mice)

Intracerebral administration of excitatory amino acids (EAA) induces such drastic overexcitation that it leads to convulsions and death of the animals (mice) within a short time. These signs can be inhibited by systemic, e.g. intraperitoneal, administration of centrally acting substances (EAA antagonists). Since excessive activation of EAA receptors in the central nervous system plays a significant part in the pathogenesis of various neurological disorders, it is possible to infer from the detected EAA antagonism in vivo that the substances may have therapeutic uses for such CNS disorders. As a measure of the efficacy of the substances, an ED_{50} was determined, at which 50% of the animals are free of signs, owing to the previous i.p. administration of the measured substance, by a fixed dose of either NMDA or AMPA.

The amides I with heterocyclic substituents are inhibitors of cysteine derivatives [sic] such as calpain I and II and cathepsin B and L, and can thus be used to control diseases associated with an elevated activity of calpain enzymes or cathepsin enzymes. The present amides I can accordingly be used to treat neurodegenerative disorders occurring after ischemia, trauma, subarachnoid hemorrhages and stroke, and neurodegenerative disorders such as multi-infarct dementia, Alzheimer's disease, Huntington's disease and epilepsies and, in addition, to treat damage to the heart after cardiac ischemia, damage to the kidneys after renal ischemia, skeletal muscle damage, muscular dystrophies, damage caused by proliferation of smooth muscle cells, coronary vasospasms, cerebral vasospasms, cataracts of the eyes, restenosis of the blood vessels after angioplasty. In addition, the amides I may be useful in the chemotherapy of tumors and metastasis thereof and for treating disorders in which an elevated interleukin-1 level occurs, such as inflammation and rheumatic disorders.

The pharmaceutical preparations according to the invention comprise a therapeutically effective amount of the compounds I in addition to conventional pharmaceutical ancillary substances.

The active ingredients can be present in the usual concentrations for local external use, for example in dusting powders, ointments or sprays. As a rule, the active ingredients are present in an amount of from 0.001 to 1% by weight, preferably 0.001 to 0.1% by weight.

For internal use, the preparations are administered in single doses. From 0.1 to 100 mg are given per kg of body weight in a single dose. The preparation may be administered in one or more doses each day, depending on the nature and severity of the disorders.

The pharmaceutical preparations according to the invention comprise, apart from the active ingredient, the customary excipients and diluents appropriate for the required mode of administration. For local external use it is possible to use pharmaceutical ancillary substances such as ethanol, isopropanol, ethoxylated castor oil, ethoxylated hydrogenated castor oil, polyacrylic acid, polyethylene glycol, polyethylene glyco [sic] stearate, ethoxylated fatty alcohols, liquid paraffin, petrolatum and wool fat. Suitable examples for internal use are lactose, propylene glycol, ethanol, starch, talc and polyvinylpyrrolidone.

It is also possible for antioxidants such as tocopherol and butylated hydroxyanisole, and butylated hydroxytoluene, flavor-improving additives, stabilizers, emulsifiers and lubricants to be present.

The substances which are present in the preparation in addition to the active ingredient, and the substances used in producing the pharmaceutical preparations, are toxicologically acceptable and compatible with the active ingredient in each case. The pharmaceutical preparations are produced in a conventional way, for example by mixing the active ingredient with other [sic] customary excipients and diluents.

The pharmaceutical preparations can be administered in various ways, for example orally, parenterally, such as intravenously by infusion, subcutaneously, intraperitoneally and topically. Thus, possible presentations are tablets, emulsions, solutions for infusion and injection, pastes, ointments, gels, creams, lotions, dusting powders and sprays.

Examples

Example 1

2-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

a) Methyl 2-(4-phenyl-1-piperazinylmethyl)benzoate

10.0 g of methyl 2-chloromethylbenzoate, 15 g of potassium carbonate, 8.8 g of N-phenylpiperazine and a spatula-tip of 18-crown-6 in 200 ml of DMF were heated at 100°C for 5 h and then stirred at room temperature for 60 h. The excess potassium carbonate was filtered off, the filtrate was concentrated, and the residue was partitioned between water and ethyl acetate. Drying of the organic phase over magnesium sulfate and removal of the solvent resulted in 16.8 g (100%) of the product.

b) 2-(4-phenyl-1-piperazinylmethyl)benzoic acid

16.8 g of intermediate 1a were introduced into 150 ml of THF, and 1.7 g of LiOH in 150 ml of water were added at room temperature. The cloudy solution was clarified by adding 10 ml of MeOH. The reaction mixture was stirred at room temperature for 12 h and hydrolyzed with an equimolar amount of 1 M HCl. The reaction mixture was evaporated to dryness, and the residue was taken up in methanol/toluene. Removal of the solvent resulted in 15.2 g (86%) of the product, which still contained salt.

c) 2-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-ol-2-yl)amide

3.0 g of intermediate 1b and 3 ml of triethylamine were introduced into 50 ml of DMF. 5 g of sodium sulfate were added and the mixture was stirred for 30 min. 1.5 g of phenylalaninol, 1.4 g of HOBT and 2.1 g of EDC were successively added at 0°C, and the mixture was stirred at room temperature overnight. The reaction mixture was poured into distilled water, made alkaline with $NaHCO_3$, saturated with NaCl and extracted three times with 100 ml of methylene chloride. The organic phases were washed twice with water and dried over magnesium sulfate. Removal of the solvent resulted in 2.5 g (59%) of the product.

d) 2-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

2.3 g of intermediate 1c were introduced into 50 ml of DMSO in the presence of 2.4 g of triethylamine, and 2.5 g of SO_3/pyridine complex were added. The mixture was stirred at room temperature overnight. The mixture was poured into 250 ml of distilled water, made alkaline with $NaHCO_3$, saturated with NaCl and extracted with 100 ml of methylene chloride, and the organic phase was dried over magnesium sulfate. After removal of the solvent, the residue was dissolved in THF, and the hydrochloride was precipitated with HCl in dioxane. The precipitate was filtered off with suction and washed several times with ether, resulting in 1.9 g (71%) of the product.

^{1}H-NMR (d_6-DMSO): δ = 2.9 (2H), 3.0-3.3 (8H), 4.1-4.5 (2H), 4.7 (1H), 6.8-7.7 (14H), 9.3 (1H), 9.8 (1H) ppm.

Example 2

2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

a) Methyl 2-((4-benzyl-1-piperazinyl)methyl)benzoate [sic]

10.0 g of methyl 2-chlorobenzoate and 9.6 g of N-benzylpiperazine were reacted in 200 ml of DMF in the presence of 15 g of potassium carbonate at 100°C in analogy to Example 1a, resulting in 17.6 g (100%) of the product.

b) 2-((4-Benzyl-1-piperazinyl)methyl)benzoic [sic] acid

17.5 g of intermediate 2a in 150 ml of THF were hydrolyzed with 1.6 g of LiOH in 150 ml of water in analogy to Example 1b, resulting in 9.1 g (54%) of the product.

c) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-ol-2-yl)amide

3.0 g of intermediate 2b were reacted in 60 ml of DMF with 3 ml of triethylamine, 1.5 g of phenylalaninol, 1.3 g of HOBT and 2.0 g of EDC in analogy to Example 1c, resulting in 2.0 g (46%) of the product.

d) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

1.5 g of intermediate 2c were oxidized in 40 ml of DMSO with 1.9 g of SO_3/pyridine complex in 20 ml of DMSO in the presence of 2.3 ml of triethylamine in analogy to Example 1d, resulting in 0.4 g (21%) of the product in the form of the fumarate.

^{1}H-NMR (d_6-DMSO): δ = 2.1-2.3 (8H), 2.9-3.0 (1H), 3.3-3.6 (6H), 4.5 (1H), 6.6 (2H), 7.1-7.7 (14H), 9.7 (1H), 10.3 (1H) ppm.

Example 3

2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

a) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-ol-3-phenylpropan-2-yl)amide

1.5 g of intermediate 2b were reacted in 40 ml of DMF with 0.7 ml of triethylamine, 1.0 g of 3-amino-2-hydroxy-4-phenylbutyramide hydrochloride, 0.6 g of HOBT and 0.9 g of EDC in analogy to Example 1c, resulting in 0.8 g (38%) of the product.

b) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

0.7 g of intermediate 3a were oxidized in 20 ml of DMSO with 0.7 g of SO_3/pyridine complex in the presence of 0.8 g of triethylamine in analogy to Example 1d, resulting in 0.1 g (18%) of the product in the form of the free base.

^{1}H-NMR (d_6-DMSO): δ = 2.3 (4H), 2.8-3.5 (8H), 5.3 (1H), 6.7-7.5 (16H), 7.8 (1H), 8.1 (1H), 10.3 (1H) ppm.

Example 4

2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

a) Methyl 2-(4-((3-methylphenyl)-1-piperazinyl)-methyl)benzoate [sic]

4.0 g of methyl 2-chloromethylbenzoate and 4.4 g of 3-methylphenylpiperazine were heated in 200 ml of DMF in the presence of 4.5 g of potassium carbonate at 140°C for 3 h. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic phases were washed three times with saturated brine, dried over magnesium sulfate and concentrated, resulting in 6.5 g (92%) of the product.

b) 2-(4-((3-Methylphenyl)-1-piperazinyl)methyl)-benzoic [sic] acid

5.9 g of intermediate 4a were dissolved in 75 ml of THF and hydrolyzed with 0.9 g of LiOH in 75 ml of water in analogy to Example 1b, resulting in 2.9 g (51%) of the product.

c) 2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)-benzoic acid N-(1-carbamoyl-1-ol-3-phenylpropan-2-yl)amide

1.8 g of intermediate 4b were introduced into 50 ml of DMF in the presence of 2.7 ml of triethylamine, and 0.8 g of HOBT, 1.3 g of 3-amino-2-hydroxy-4-phenylbutyramide hydrochloride and 1.2 g of EDC were successively added, in analogy to Example 1c, resulting in 1.4 g (50%) of the product.

d) 2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)-benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

1.2 g of intermediate 4c were dissolved in 30 ml of DMSO and oxidized with 1.6 g of SO_3/pyridine

complex in the presence of 1.5 ml of triethylamine in analogy to Example 1d, resulting in 1.0 g (83%) of the product.

MS: m/e = 484 (M^+)

Examples 5 and 6 were synthesized in analogy to Example 1.

Example 5

3-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide fumarate

^{1}H-NMR (d_6-DMSO): δ = 2.5 (4H), 2.9 (1H), 3.2 (4H), 3.3 (1H), 3.7 (2H), 4.5 (1H), 6.6 (2H), 6.75 (1H), 6.9 (2H), 7.2 (2H), 7.2-7.3 (5H), 7.45 (1H), 7.55 (1H), 7.75 (1H), 7.8 (2H), 8.9 (1H), 9.7 (1H) ppm.

Example 6

3-((4-(2-tert-Butyl-4-trifluoromethylpyrimidin-6-yl)-homopiperazin-1-yl)methyl)benzoic acid N-(3-phenyl-propan-1-al-2-yl)amide

MS: m/e = 568 (M^++1)

Example 7

4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)-benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

a) 4-(N-(3,4-Dioxomethylene)benzyl-N-methylamino-methyl)benzoic acid

11.5 g of N-(3,4-dioxomethylene)benzyl-N-methylamine and 15.5 g of triethylamine were introduced into [lacuna], and 15.0 g of 4-bromomethylbenzoic acid in 100 ml of THF were

added. The reaction mixture was briefly heated to reflux and then stirred at room temperature for 15 h. After filtering off the salts, the mother liquor was concentrated, and the residue was dissolved in ethyl acetate and washed with water. The aqueous phase was made alkaline and extracted several times with ethyl acetate, resulting in 6.6 g (32%) of the product as a white solid.

b) 4-(N-(3,4-Dioxomethylene)benzyl-N-methylamino-methyl)benzoic acid N-(3-phenylpropan-1-ol-2-yl)-amide

4.4 g of intermediate 5a [sic] were introduced into 50 ml of DMF in the presence of 2.9 g of triethylamine, and 1.8 g of HOBT, 2.0 g of phenylalaninol and 2.8 g of EDC were successively added, in analogy to Example 1c, resulting in 2.3 g (40%) of the product.

c) 4-(N-(3,4-Dioxomethylene)benzyl-N-methylamino-methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)-amide

2.0 g of intermediate 5b [sic] were dissolved in 60 ml of DMSO and oxidized with 2.1 g of SO_3/pyridine complex in the presence of 1.8 ml of triethylamine in analogy to Example 1d, resulting in 1.3 g (68%) of the product.

^{1}H-NMR (CF_3COOD): δ = 2.9 (3H), 3.2 (2H), 4.3-4.9 (5H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.2-7.4 (5H), 7.8 (2H), 8.25 (2H) ppm.

MS: m/e = 430 (M^+)

Examples 8-28 were prepared in analogy to Example 7.

Example 8

4-(N-Benzyl-N-methylaminomethyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

^{1}H-NMR (CF_3COOD): δ = 2.9 (3H), 3.2 (2H), 4.3-5.0 (5H), 6.7 (1H), 7.25-7.5 (8H), 7.55 (2H), 7.8 (2H), 8.2 (2H) ppm.

MS: m/e = 386 (M^+)

Example 9

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

^{1}H-NMR (CF_3COOD): δ = 2.9 (3H), 3.3 (2H), 4.0 (3H), 4.3-4.9 (5H), 6.7 (1H), 7.1-7.4 (7H), 7.5 (2H), 7.8 (2H), 8.2 (2H) ppm.

MS: m/e = 416 (M^+)

Example 10

4-(N-Benzyl-N-methylaminomethyl)benzoic acid N-(3-butan-1-al-2-yl)amide

^{1}H-NMR (CF_3COOD): δ = 1.1 (3H), 1.6 (2H), 2.0 (2H), 2.9 (3H), 4.3-4.5 (3H), 4.7 (1H), 4.8 (1H), 6.6 (1H), 7.3-7.6 (5H), 7.8 (2H), 8.3 (2H) ppm.

MS: m/e = 338 (M^+)

Example 11

4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)-benzoic acid N-(3-butan-1-al-2-yl)amide

^{1}H-NMR (CF_3COOD): δ = 1.1 (3H), 1.6 (2H), 1.9 (2H), 2.9 (3H), 4.25-4.6 (4H), 4.75 (1H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.8 (2H), 8.3 (2H) ppm.

MS: m/e = 382 (M^+)

Example 12

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoic acid N-(3-butan-1-al-2-yl)amide

MS: m/e = 368 (M^+)

Example 13

4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)-benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

^{1}H-NMR (CF_3COOD): δ = 1.0-2.0 (13H), 2.9 (3H), 4.3-4.9 (4H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.8 (2H), 8.3 (2H) ppm.

MS: m/e = 436 (M^+)

Example 14

4-(N-(4-Benzyl-N-methylaminomethyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 1.0-1.8 (13H), 2.1 (3H), 3.4 (2H), 3.5 (2H), 4.3 (1H), 7.1-7.4 (5H), 7.5 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

Example 15

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

^{1}H-NMR ($CDCl_3$): δ = 1.0-1.8 (13H), 2.1 (3H), 3.4 (2H), 3.5 (2H), 3.7 (3H), 4.3 (1H), 6.8 (2H), 7.25 (2H), 7.5 (2H), 7.9 (2H), 8.8 (1H), 9.5 (1H) ppm.

Example 16

4-((2-Phenylpyrrolid-1-yl)methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

MS: m/e = 420 (M^+)

Example 17

4-((2-Phenylpyrrolid-1-yl)methyl)benzoic acid N-(3-butan-1-al-2-yl)amide

MS: m/e = 364 (M^+)

Example 18

4-((2-Phenylpyrrolid-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

MS: m/e = 412 (M^+)

Example 19

4-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

^{1}H-NMR ($CDCl_3$): δ = 1.0-1.9 (13H), 2.0 (2H), 2.8 (2H), 3.3 (2H), 4.5 (2H), 4.8 (1H), 6.4 (1H), 6.5 (2H), 7.0 (2H), 7.4 (2H), 7.8 (2H), 9.7 (1H) ppm.

MS: m/e = 404 (M^+)

Example 20

4-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 1.9 (2H), 2.75 (2H), 2.9 (1H), 3.3 (1H), 3.4 (2H), 4.4 (1H), 4.5 (2H), 6.3 (2H), 6.8 (2H), 7.1-7.25 (5H), 7.3 (2H), 7.7 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 398 (M^+)

Example 21

4-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-butan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 0.9 (3H), 1.2-2.0 (6H), 2.7 (2H), 3.3 (2H), 4.2 (1H), 4.5 (2H), 6.4 (2H), 6.8 (2H), 7.3 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 350 (M^+)

Example 22

4-((1,2,3,4-Dihydroisoquinolin-2-yl)methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 0.9-1.8 (13H), 2.7-2.9 (4H), 3.6 (2H), 3.75 (2H), 4.4 (1H), 6.9-7.1 (4H), 7.4 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 404 (M^+)

Example 23

4-((1,2,3,4-Dihydroisoquinolin-2-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 2.7 (2H), 2.8 (2H), 2.9 (1H), 3.2 (1H), 3.5 (2H), 3.7 (2H), 4.5 (1H), 6.9-7.1 (4H), 7.2-7.3 (5H), 7.5 (2H), 7.75 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 398 (M^+)

Example 24

4-((1,2,3,4-Dihydroisoquinolin-2-yl)methyl)benzoic acid N-(3-butan-1-al-2-yl)amide hydrochloride

^{1}H-NMR (d_6-DMSO): δ = 0.9 (3H), 1.2-2.0 (4H), 3.0 (1H), 3.3 (2H), 3.6 (1H), 4.1-4.6 (5H), 7.2 (4H), 7.8 (2H), 8.0 (2H), 9.0 (1H), 9.5 (1H), 11.75 (1H) ppm.

Example 25

4-((6,7-Dimethoxy-1,2,3,4-dihydroisoquinolin-2-yl)-methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)-amide

^{1}H-NMR (d_6-DMSO): δ = 0.9-1.9 (13H), 2.7 (4H), 3.4 (2H), 3.6 (3H), 3.65 (2H), 3.7 (3H), 4.3 (1H), 6.5 (1H), 6.6 (1H), 7.5 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 464 (M^+)

Example 26

4-((6,7-Dimethoxy-1,2,3,4-dihydroisoquinolin-2-yl)-methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 2.7 (4H), 2.9 (1H), 3.25 (1H), 3.6 (6H), 3.7 (2H), 4.5 (1H), 6.6 (1H), 6.7 (1H), 7.2-7.3 (5H), 7.4 (2H), 7.8 (2H), 8.9 (1H), 9.6 (1H) ppm.

MS: m/e = 458 (M^+)

Example 27

4-((6,7-Dimethoxy-1,2,3,4-dihydroisoquinolin-2-yl)-methyl)benzoic acid N-(3-butan-1-al-2-yl)amide

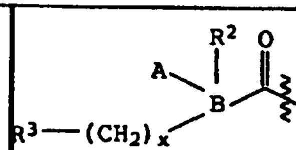
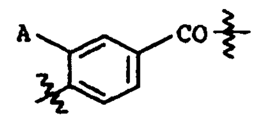
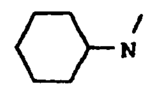
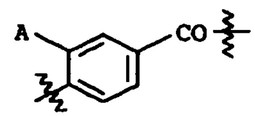
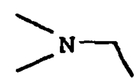
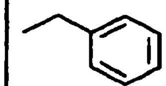
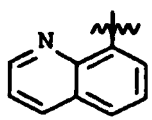
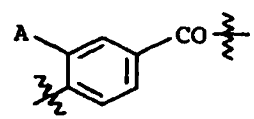
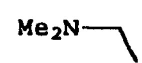
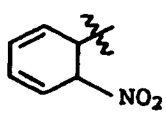
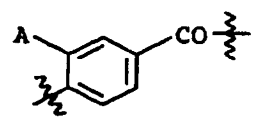
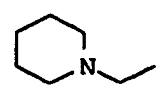
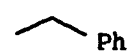
^{1}H-NMR (d_6-DMSO): δ = 0.9 (3H), 1.4 (2H), 1.5-1.8 (2H), 2.7 (4H), 3.4 (2H), 3.7 (3H), 3.75 (3H), 3.8 (2H), 4.3 (1H), 6.6 (1H), 6.7 (1H), 7.4 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

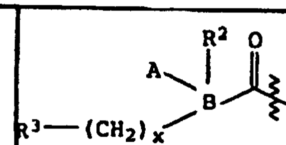
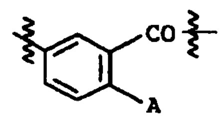
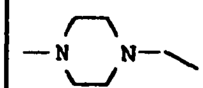
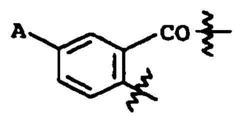
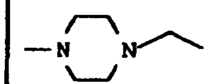
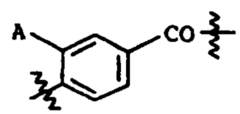
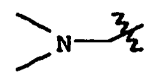
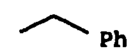
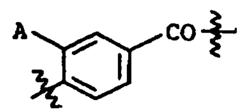
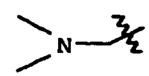
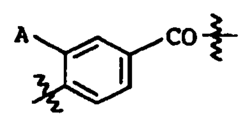
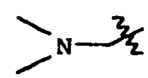
MS: m/e = 410 (M^+)

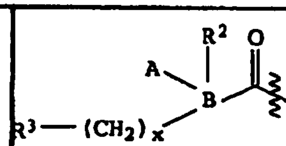
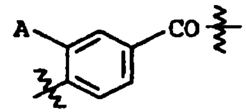
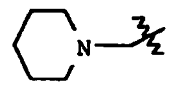
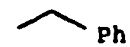
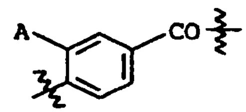
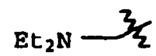
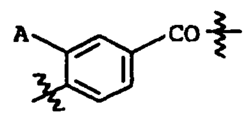
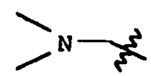
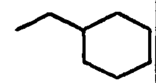
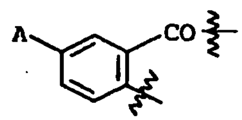
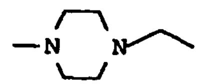
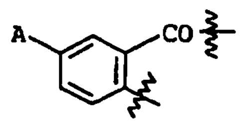
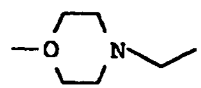
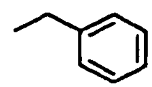
Example 28

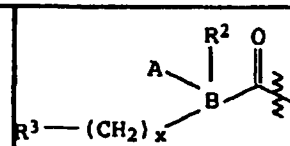
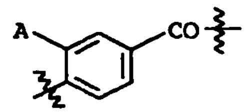
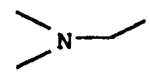
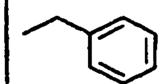
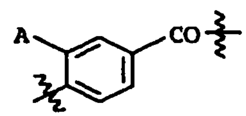
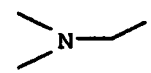
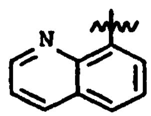
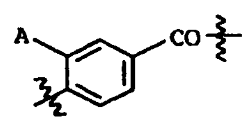
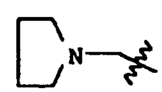
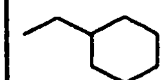
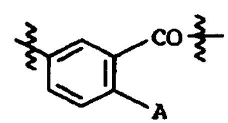
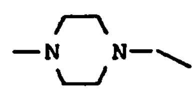
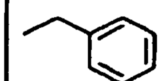
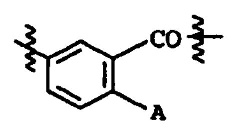
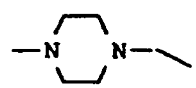
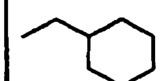
2-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-butan-1-al-2-yl)amide

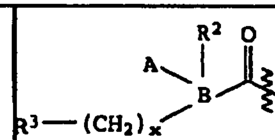
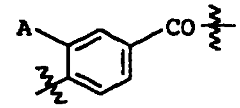
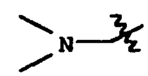
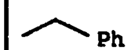
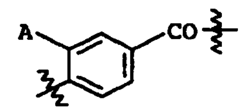
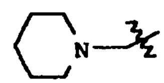
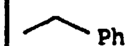
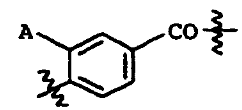
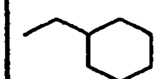
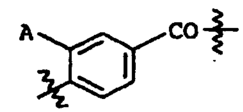
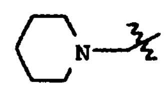
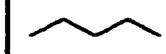
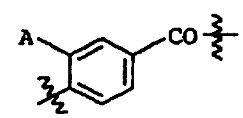
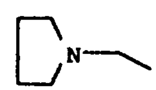
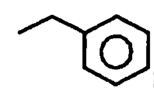
MS: m/e = 441 (M^+)

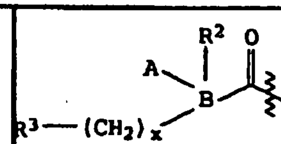
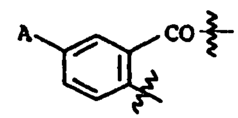
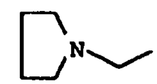
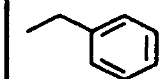
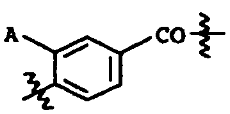
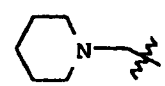
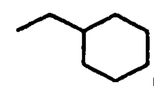
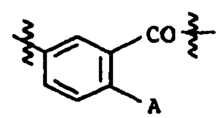
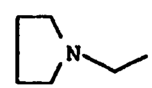
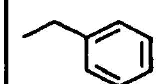
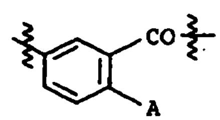
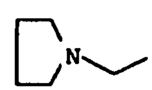
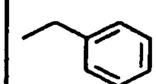
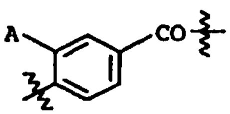
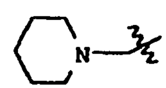
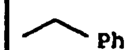
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
1	Bu	SO_2NH	H				H
2	2-Py	SO_2NH	H				H
3		SO_2NH	H				H
4		SO_2NH	H				H

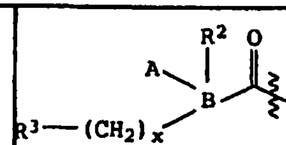
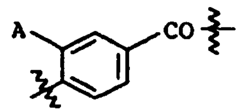
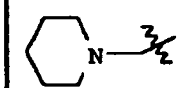
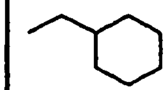
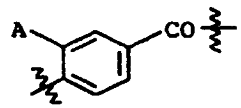
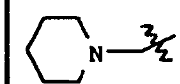
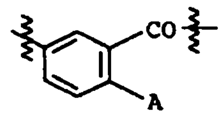
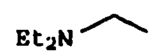
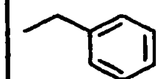
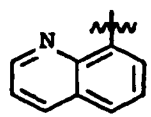
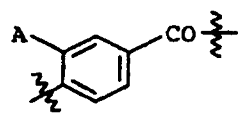
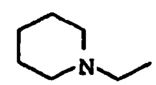
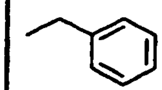
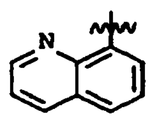
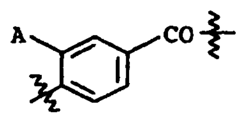
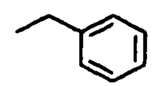
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
5	Ph	CH_2O	H				H
6	2-Py	CH_2O	H				H
7	Bu	SO_2NH	H				H
8	Naphth	SO_2NH	H				H
9	Naphth	SO_2NH	H				$CONH_2$

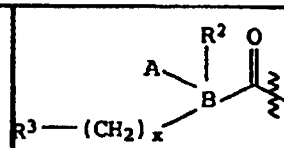
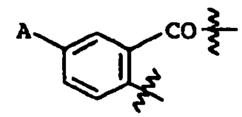
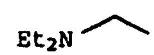
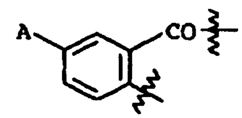
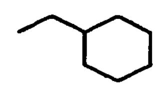
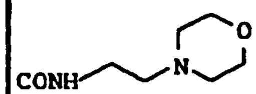
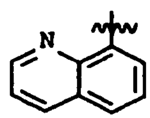
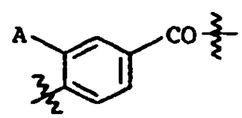
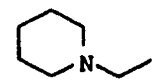
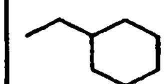
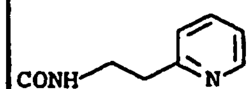
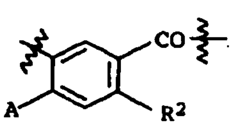
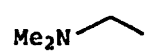
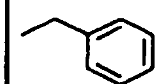
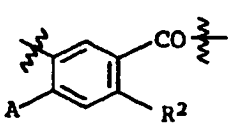
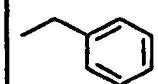
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
10	Ph	SO_2NH	H				H
11	Bu	SO_2NH	H				$CONH_2$
12	Naphth	SO_2NH	H				$CONH_2$
13	Ph	-O-	H				H
14	Ph	-S-	H				$CONH_2$

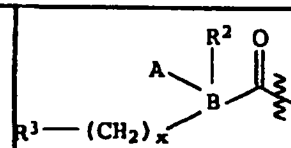
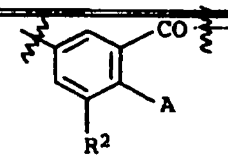
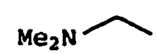
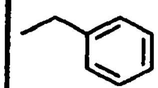
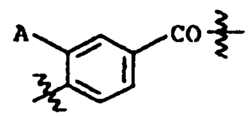
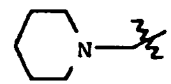
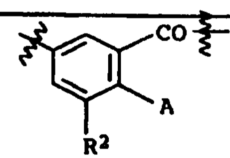
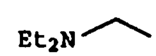
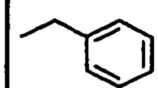
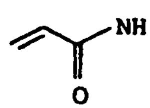
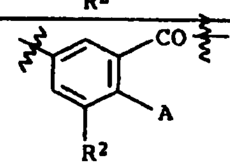
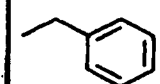
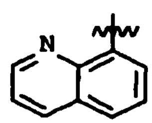
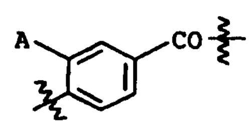
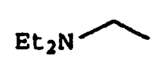
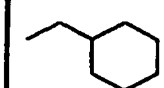
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
15	2-Py	SO_2NH	H				$CONH_2$
16	2-Py	SO_2NH	H				H
17		SO_2NH	H				H
18	Ph	-O-	H				H
19	Ph	-S-	H				$CONH_2$

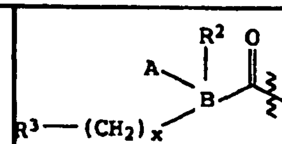
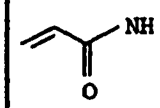
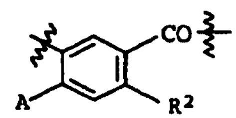
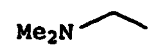
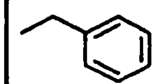
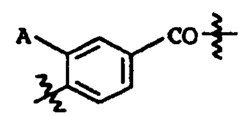
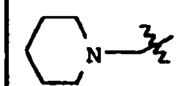
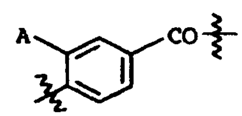
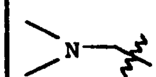
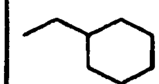
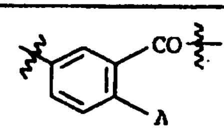
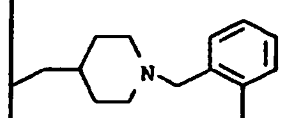
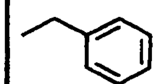
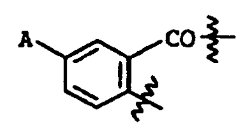
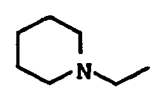
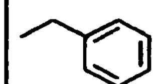
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
20	Bu	SO_2NH	H				$CONH_2$
21	Naphth	SO_2NH	H				H
22	Ph	SO_2NH	H		Et_2N		H
23	Bu	SO_2NH	H				$CONH_2$
24	2-Py	SO_2NH	H				H

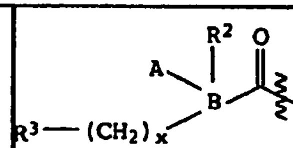
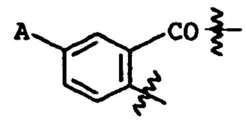
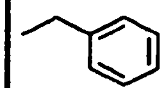
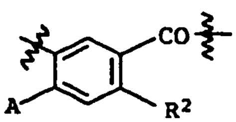
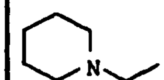
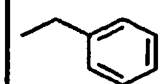
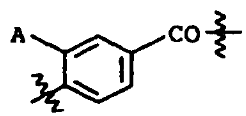
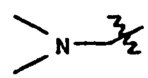
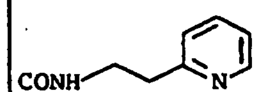
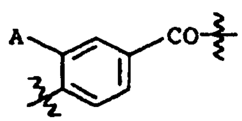
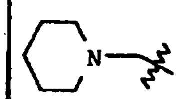
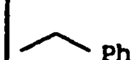
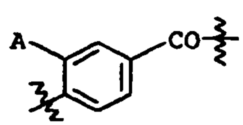
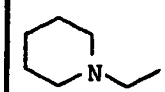
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
25	Ph	-O-	H				$CONH_2$
26	2-Py	SO_2NH	H				H
27	Ph	-O-	H				$CONH_2$
28	Ph	-O-	H				H
29	Naphth	SO_2NH	H				$CONH_2$

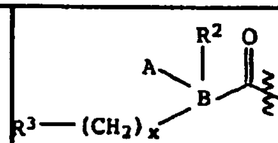
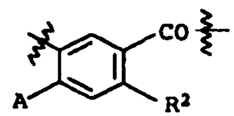
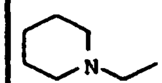
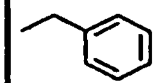
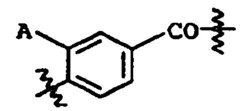
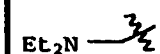
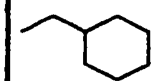
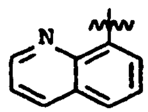
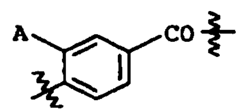
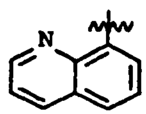
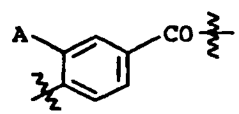
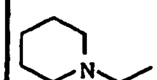
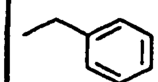
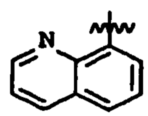
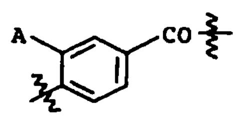
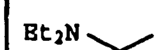
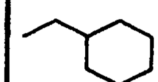
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
30	Bu	SO_2NH	H				H
31	2-Py	SO_2NH	H				$CONH_2$
32	Ph	-O-	H				H
33		SO_2NH	H				$CONH_2$
34		SO_2NH	H				H

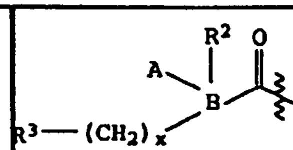
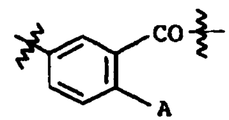
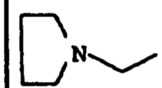
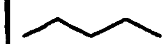
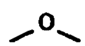
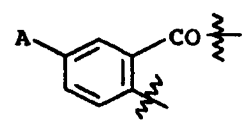
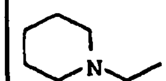
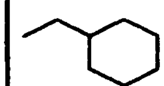
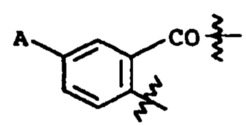
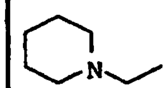
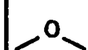
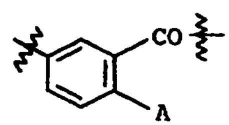
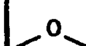
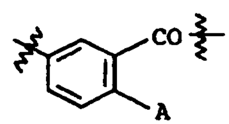
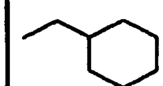
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
35	Ph	-O-	H				$CONH_2$
36	Ph	-O-	H				
37		SO_2NH	H				
38	Ph	CONH	MeO				H
39	Naphth	CONH	MeO				H

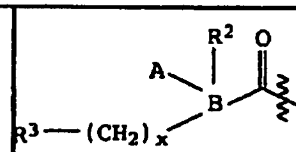
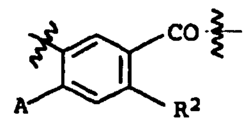
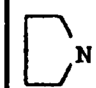
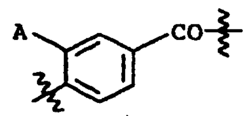
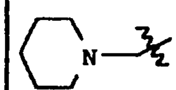
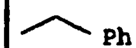
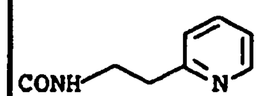
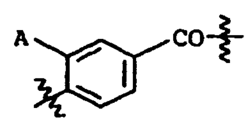
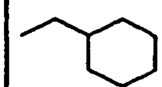
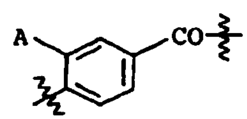
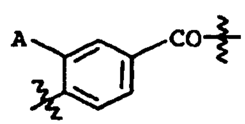
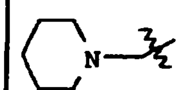
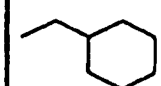
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
40	Ph	CONH	Et				H
41	Bu	SO_2NH	H				H
42	Naphth	CONH	Et				H
43	Ph		Et				H
44		SO_2NH	H				$CONH_2$

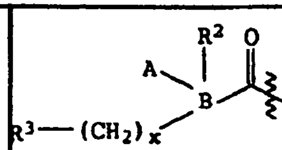
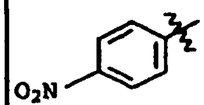
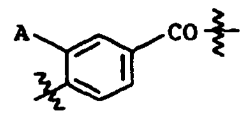
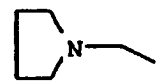
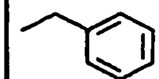
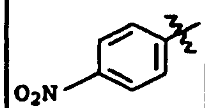
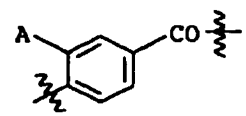
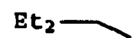
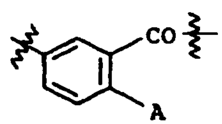
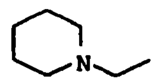
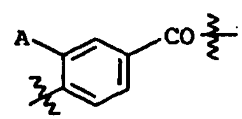
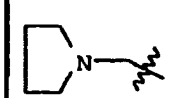
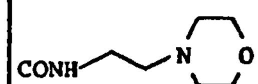
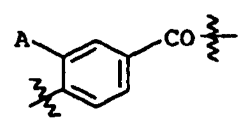
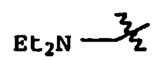
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
45	Ph		MeO				H
46	Bu	SO_2NH	H				$CONH_2$
47	Naphth	SO_2NH	H				H
48	H	m=o=O	H				H
49	Ph	-O-	H				H

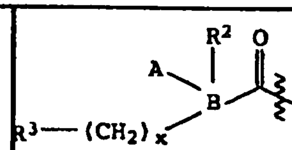
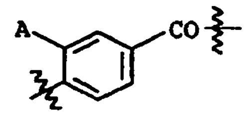
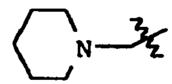
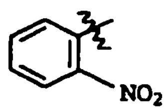
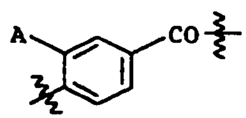
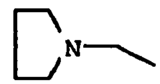
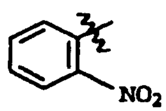
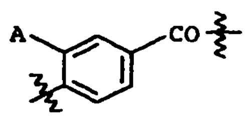
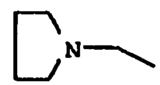
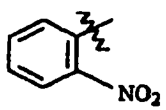
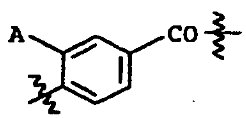
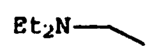
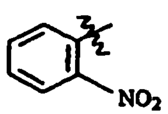
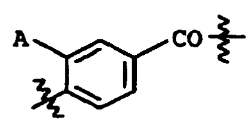
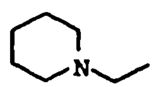
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
50	Ph	-O-	H				$CONH_2$
51	Naphth	CONH	MeO				$CONH_2$
52	Bu	SO_2NH	H				
53	Ph	SO_2NH	H				$CONH_2$
54	2-Py	SO_2NH	H				H

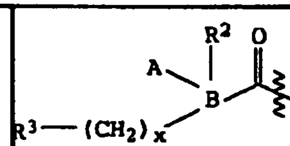
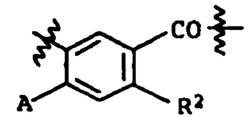
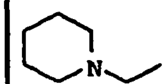
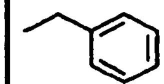
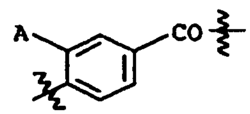
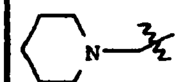
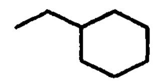
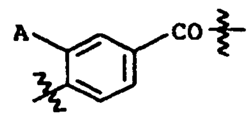
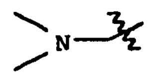
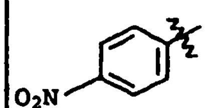
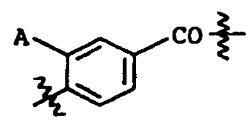
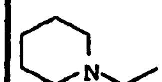
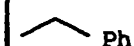
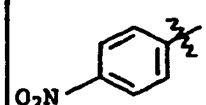
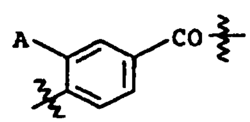
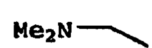
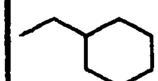
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
55	Ph	CONH	MeO				$CONH_2$
56	Bu	SO_2NH	H				H
57		SO_2NH	H		Me_2N		$CONH_2$
58		SO_2NH	H				H
59		SO_2NH	H				H

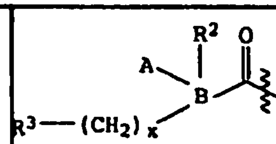
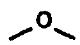
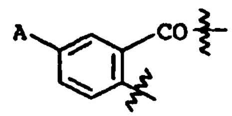
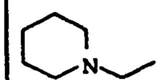
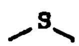
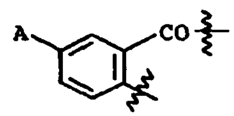
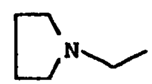
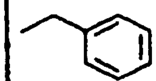
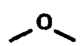
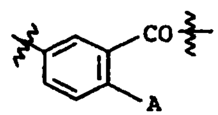
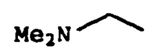
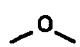
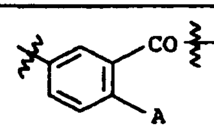
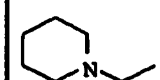
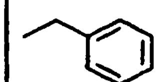
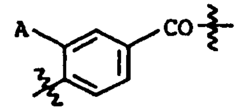
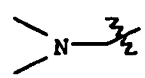
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
60	Ph	CONH	Et				$CONH_2$
61	Ph		H				H
62	Ph		H				H
63	Ph		H		Me_2N 		$CONH_2$
64	Ph		H		Me_2N 		$CONH_2$

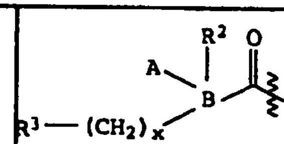
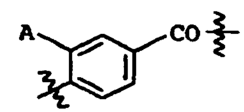
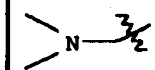
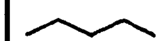
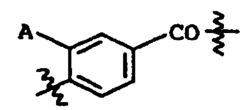
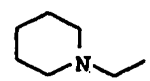
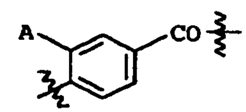
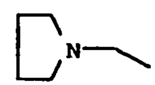
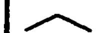
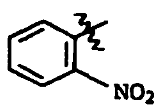
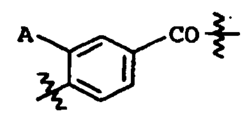
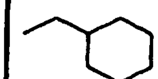
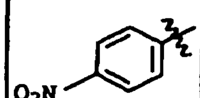
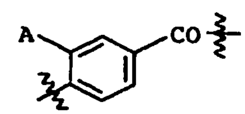
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
65	Ph	CONH	MeO				$CONH_2$
66	Ph	SO_2NH	H				
67	Ph	SO_2NH	H		Et_2N—		$CONH_2$
68	Ph	SO_2NH	H		Et_2N—		H
69	Bu	SO_2NH	H				$CONH_2$

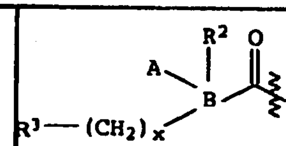
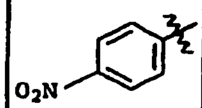
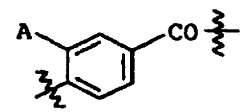
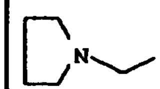
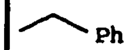
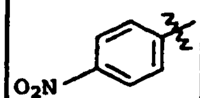
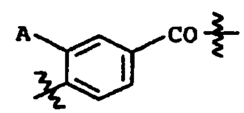
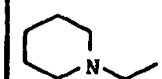
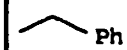
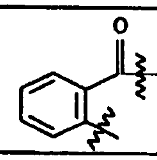
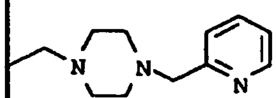
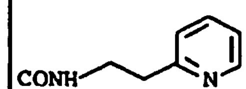
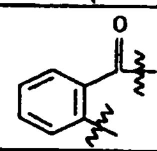
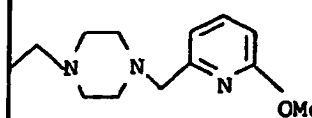
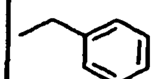
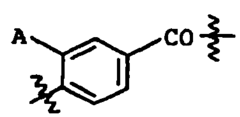
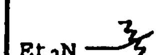
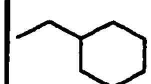
No.	R1	A	R2		R^3—$(CH_2)_x$—	R4	R5
70		SO_2NH	H				H
71		SO_2NH	H				$CONH_2$
72	Ph	CONH	Et				H
73	Bu	SO_2NH	H				
74	Ph	SO_2NH	H				$CONH_2$

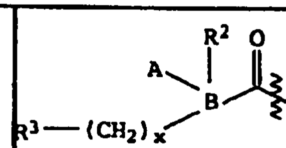
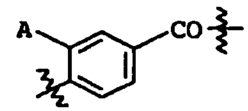
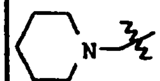
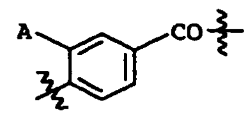
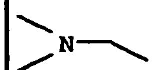
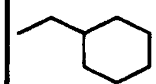
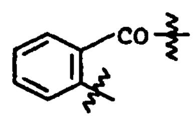
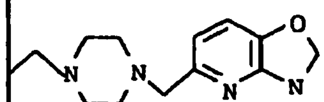
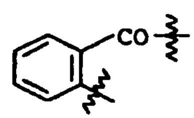
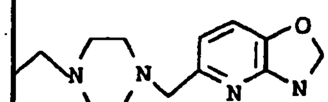
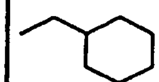
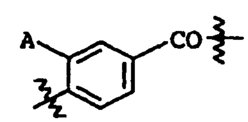
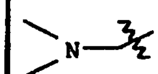
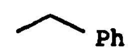
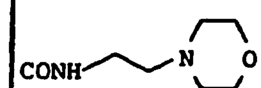
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
75	Naphtha	SO_2NH	H				H
76		SO_2NH	H				H
77		SO_2NH	H				$CONH_2$
78		SO_2NH	H				$CONH_2$
79		SO_2NH	H				$CONH_2$

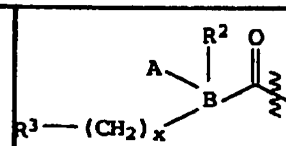
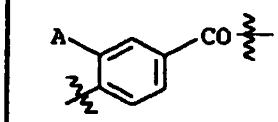
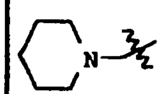
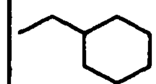
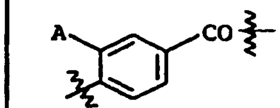
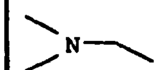
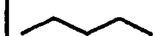
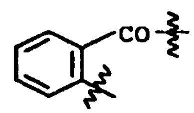
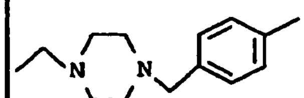
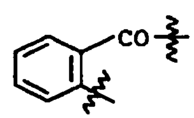
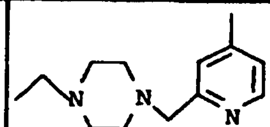
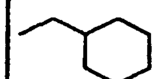
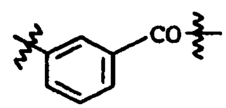
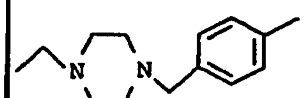
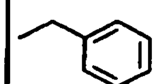
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
80	Naphth	CONH	MeO				H
81	Naphth	SO_2NH	H				$CONH_2$
82	Naphth	SO_2NH	H				H
83		SO_2NH	H				$CONH_2$
84		SO_2NH	H				$CONH_2$

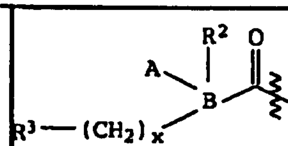
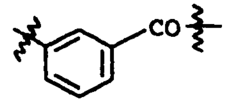
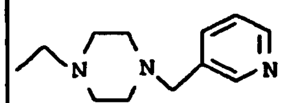
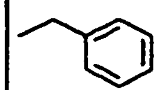
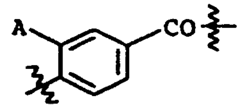
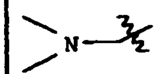
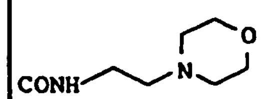
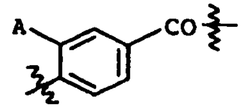
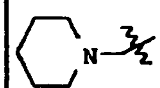
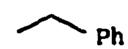
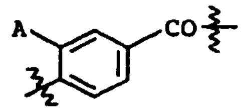
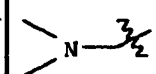
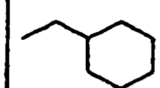
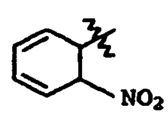
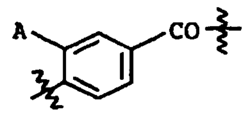
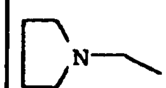
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
85	Ph		H				$CONH_2$
86	Ph		H				H
87	Ph		H				H
88	Ph		H				$CONH_2$
89	Ph	SO_2NH	H				$CONH_2$

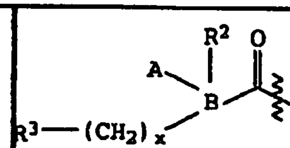
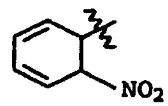
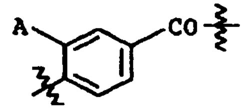
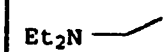
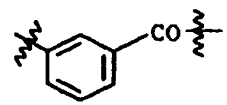
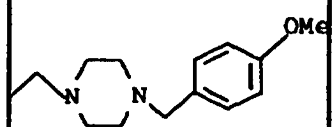
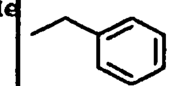
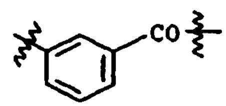
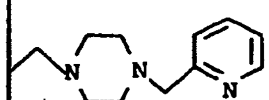
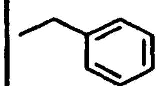
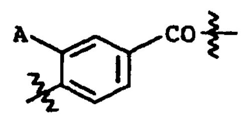
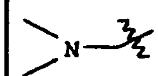
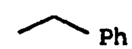
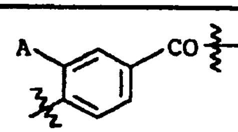
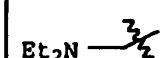
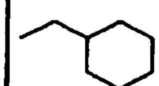
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
90	Naphth	SO_2NH	H				H
91	2-Py	SO_2NH	H			 Ph	H
92	2-Py	SO_2NH	H			 Ph	$CONH_2$
93		SO_2NH	H		Me_2N 		$CONH_2$
94		SO_2NH	H		Et_2N 		H

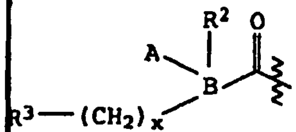
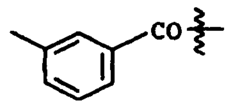
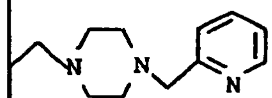
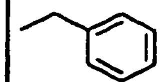
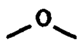
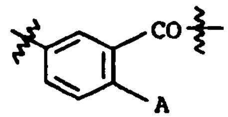
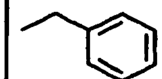
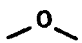
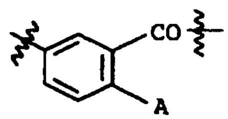
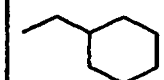
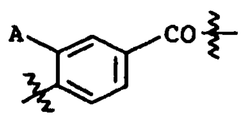
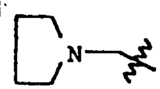
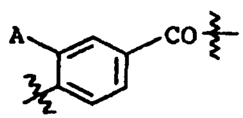
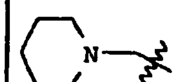
No.	R^1	A	R^2		R^3 — $(CH_2)_x$ —	R^4	R^5
95		SO_2NH	H				$CONH_2$
96		SO_2NH	H				H
97	H	m=o=o	H				
98	H	m=o=o	H				$CONH_2$
99	Bu	SO_2NH	H				$CONH_2$

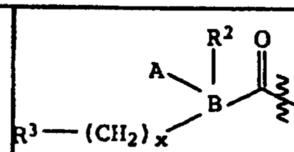
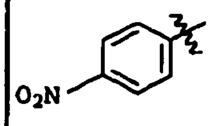
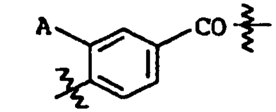
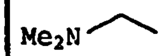
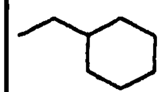
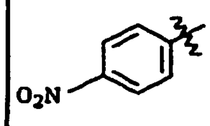
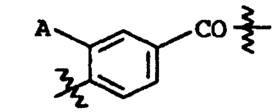
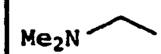
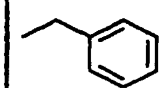
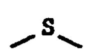
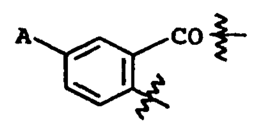
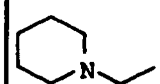
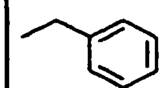
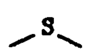
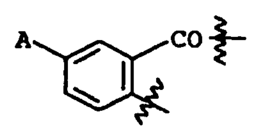
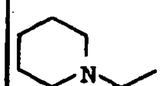
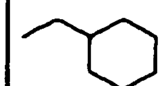
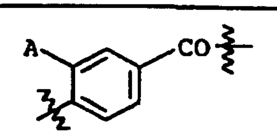
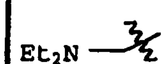
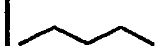
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
100	Ph	SO_2NH	H				H
101	2-Py	SO_2NH	H				$CONH_2$
102	H	m=o=O	H				H
103	H	m=o=O	H				H
104	Bu	SO_2NH	H				

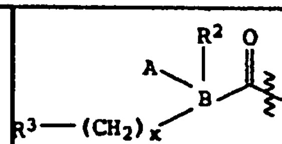
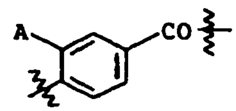
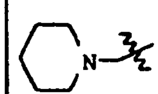
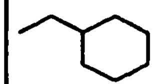
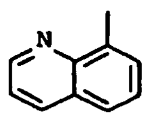
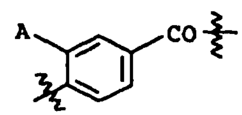
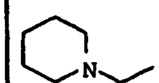
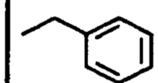
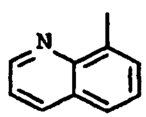
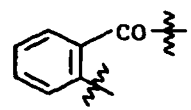
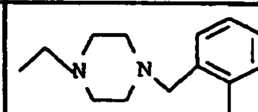
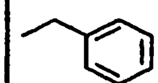
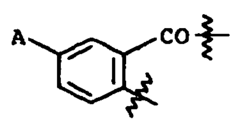
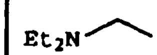
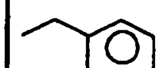
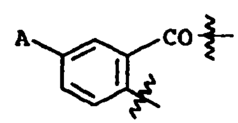
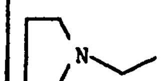
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
105	Ph	SO_2NH	H				H
106	2-Py	SO_2NH	H				$CONH_2$
107	H	m=o=O	H				$CONH_2$
108	H	m=o=O	H				$CONH_2$
109	H	m=o=O	H				H

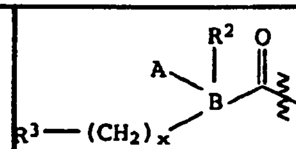
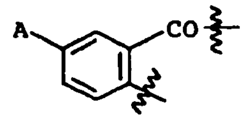
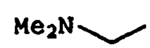
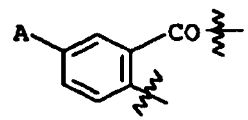
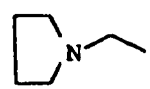
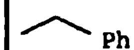
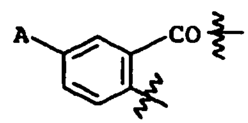
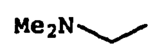
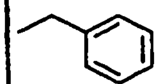
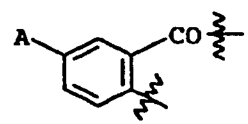
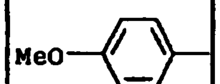
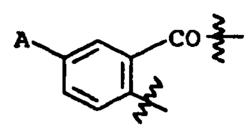
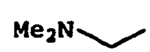
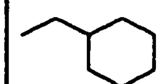
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
110	H	m=o=O	H				H
111	Ph	SO_2NH	H				
112	Ph	SO_2NH	H				$CONH_2$
113	2-Py	SO_2NH	H				H
114		SO_2NH	H				$CONH_2$

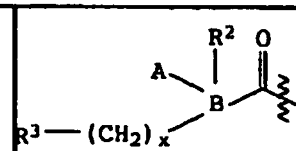
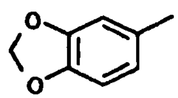
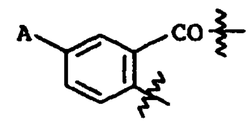
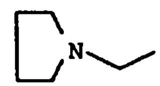
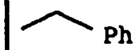
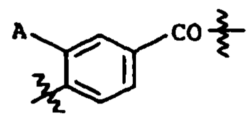
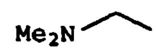
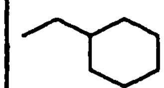
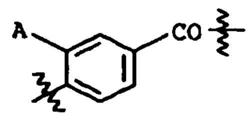
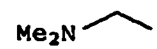
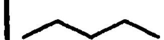
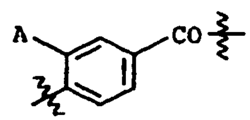
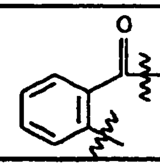
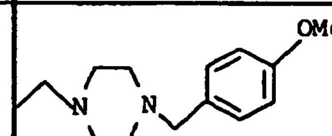
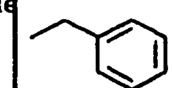
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
115		SO_2NH	H				H
116	H	m=o=O	H				H
117	H	m=o=O	H				H
118	Ph	SO_2NH	H				H
119	Naphth	SO_2NH	H				$CONH_2$

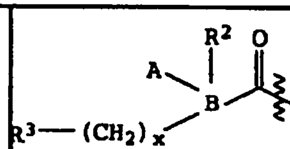
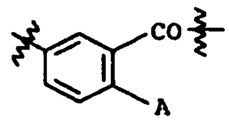
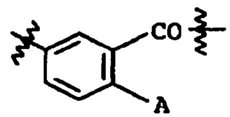
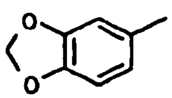
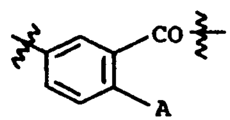
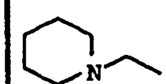
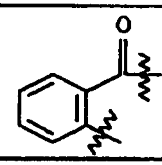
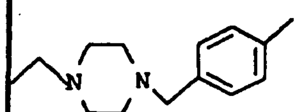
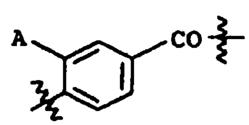
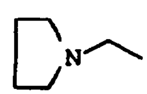
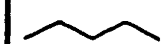
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
120	H	$SONH_2$	H				H
121	Ph		H				H
122	Ph		H				H
123	Ph	SO_2NH	H				H
124	Naphth	SO_2NH	H				$CONH_2$

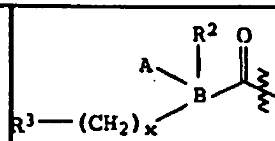
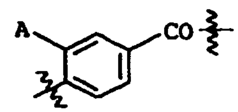
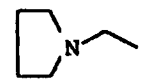
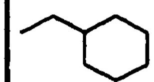
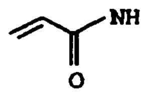
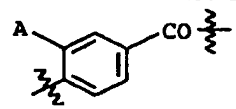
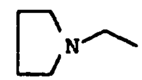
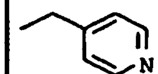
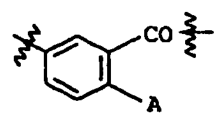
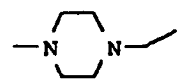
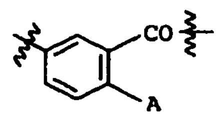
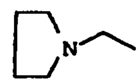
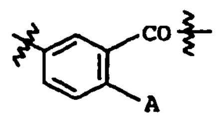
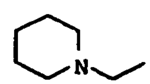
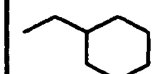
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
125		SO_2NH	H				H
126		SO_2NH	H				$CONH_2$
127	Ph		H				$CONH_2$
128	Ph		H				$CONH_2$
129	Bu	SO_2NH	H				H

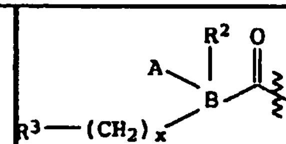
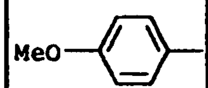
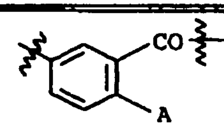
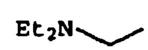
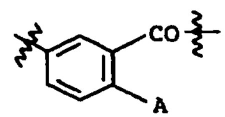
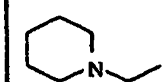
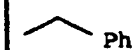
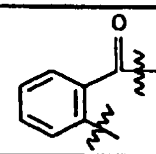
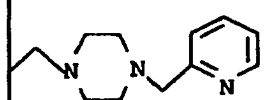
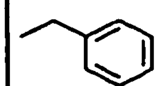
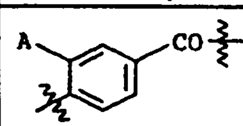
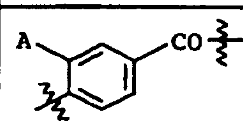
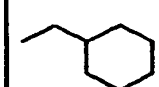
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
130	Ph	SO_2NH	H				$CONH_2$
131		SO_2NH	H				$CONH_2$
132		m=o=O	H				$CONH_2$
133	Ph	CH_2O	H				$CONH_2$
134	2-Py	CH_2O	H				$CONH_2$

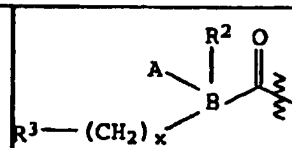
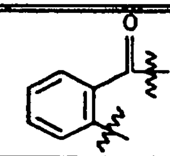
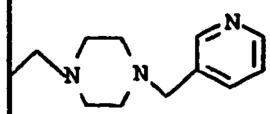
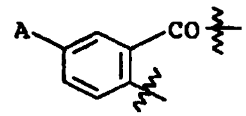
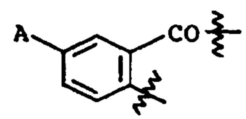
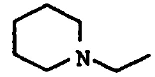
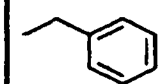
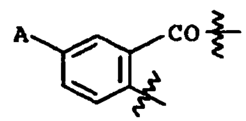
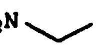
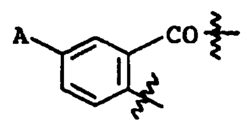
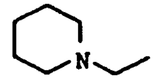
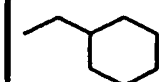
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
135	3-Py	CH_2O	H				$CONH_2$
136	4-Py	CH_2O	H				H
137	2-Tol	CH_2O	H				H
138	3-Tol	CH_2O	H				H
139		CH_2O	H				$CONH_2$

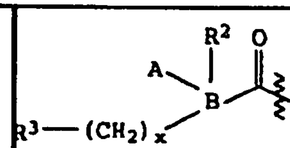
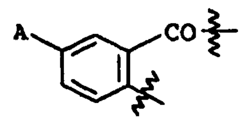
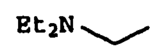
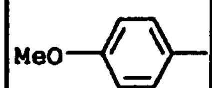
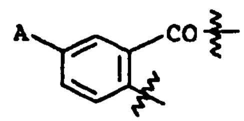
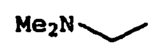
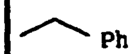
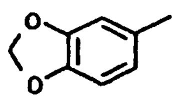
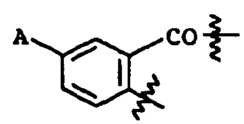
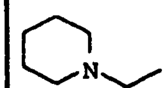
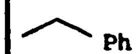
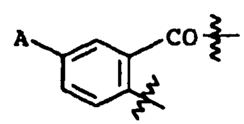
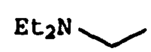
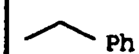
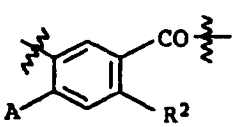
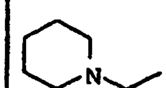
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
140		CH_2O	H				H
141	Ph	$CONH_2$	H				$CONH_2$
142	Naphth	$CONH_2$	H				$CONH_2$
143	Naphth	$CONH_2$	H		Et_2N		$CONH_2$
144	H	m=o=O	H				$CONH_2$

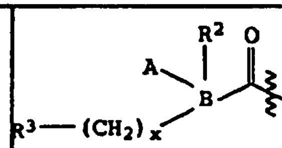
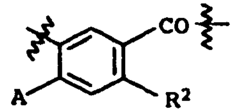
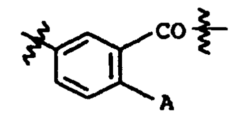
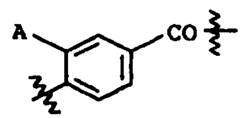
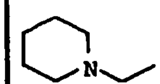
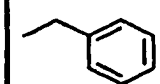
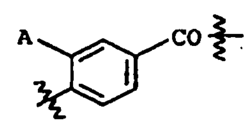
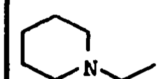
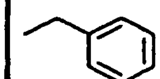
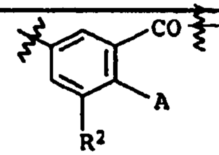
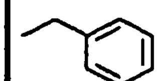
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
145	2-Py	CH_2O	H		Me_2N 	 Ph	H
146	3-Py	CH_2O	H		Et_2N 		$CONH_2$
147		CH_2O	H			 Ph	H
148	H	m=o=O	H			 Ph	H
149	Ph	CONH	H				H

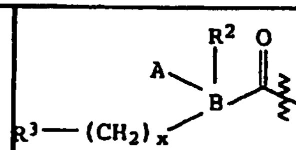
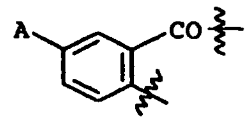
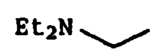
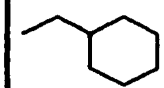
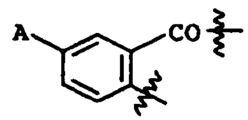
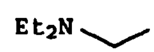
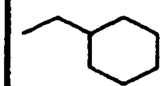
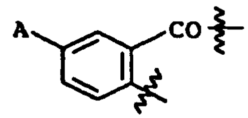
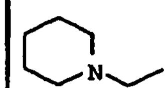
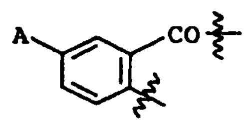
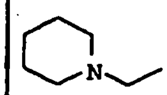
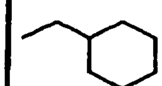
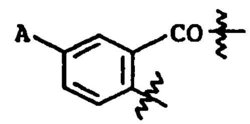
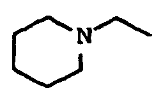
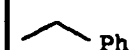
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
150	Naphth	CONH	H				H
151	Ph		H				H
152	4-Py	CH_2O	H				$CONH_2$
153	2-Tol	CH_2O	H				H
154	3-Tol	CH_2O	H				$CONH_2$

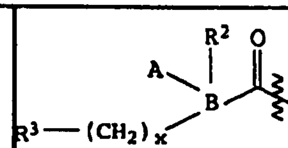
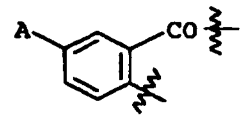
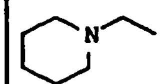
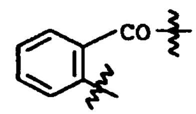
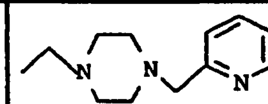
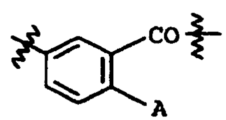
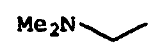
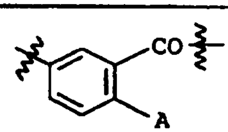
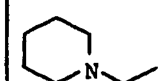
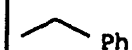
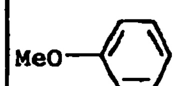
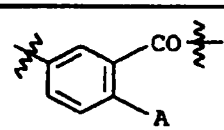
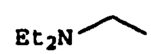
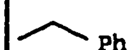
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
155		CH_2O	H				H
156	Ph	CH_2O	H				$CONH_2$
157	H	m=o=O	H				$CONH_2$
158	Naphth	CONH	H		Me_2N		H
159	Ph	CONH	H		Me_2N		$CONH_2$

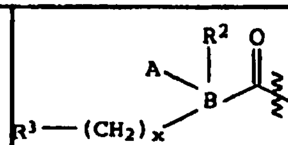
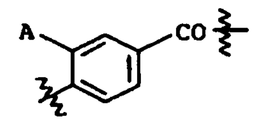
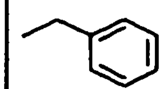
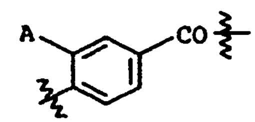
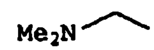
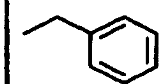
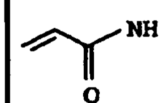
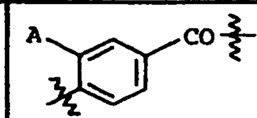
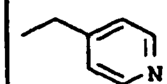
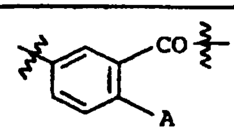
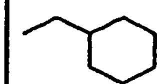
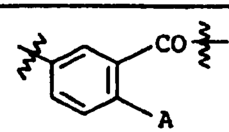
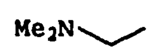
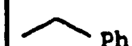
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
160	H	m=o=O	H				H
161	Ph	CH_2O	H		Et_2N 		H
162	2-Py	CH_2O	H				H
163	2-Tol	CH_2O	H		Me_2N 	 Ph	$CONH_2$
164	3-Py	CH_2O	H				H

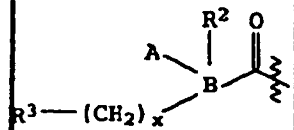
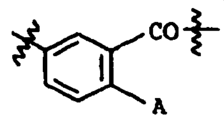
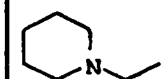
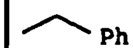
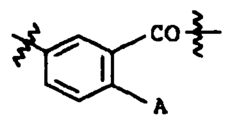
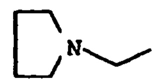
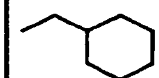
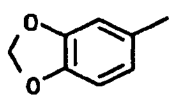
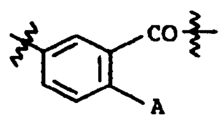
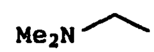
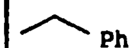
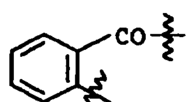
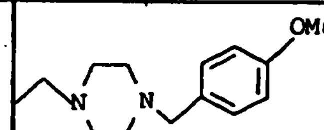
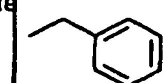
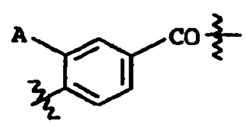
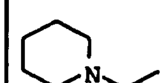
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
165	3-Tol	CH_2O	H				$CONH_2$
166		CH_2O	H				H
167		CH_2O	H				H
168	4-Py	CH_2O	H				$CONH_2$
169	Ph	SO_2NH	MeO				H

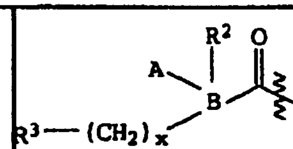
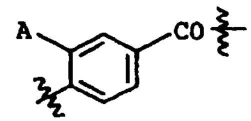
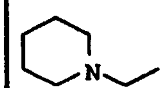
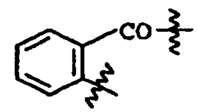
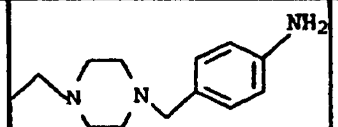
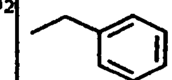
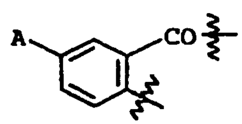
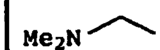
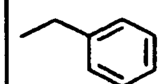
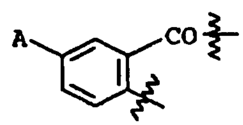
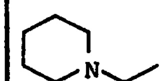
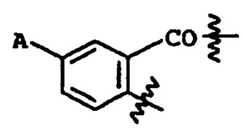
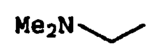
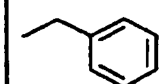
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
170	Naphth	SO_2NH	MeO				H
171	3-Tol	CH_2O	H				$CONH_2$
172	Ph	CONH	H				H
173	Naphth	CONH	H				H
174	Bu	SO_2NH	Et				$CONH_2$

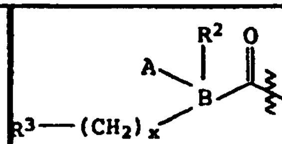
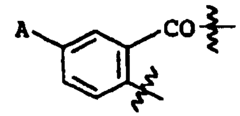
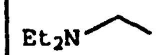
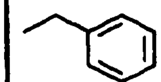
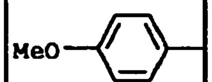
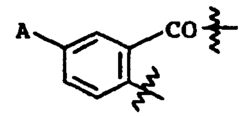
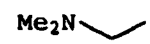
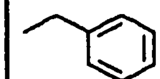
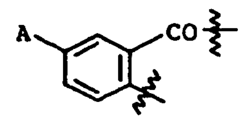
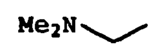
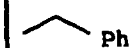
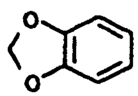
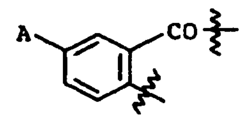
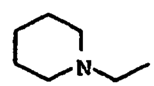
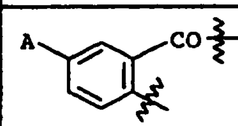
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
175	3-Tol	CH_2O	H				H
176	3-Tol	CH_2O	H				$CONH_2$
177	4-Py	CH_2O	H				H
178	4-Py	CH_2O	H				H
179	Ph	CH_2O	H				$CONH_2$

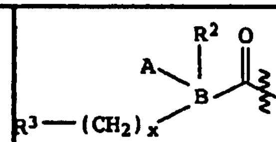
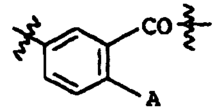
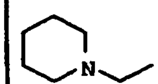
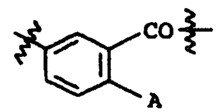
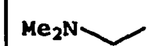
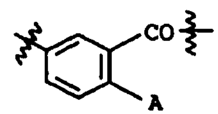
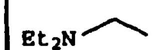
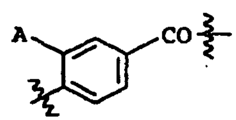
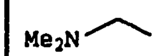
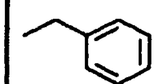
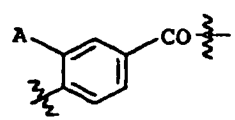
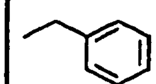
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
180	Ph	CH_2O	H				$CONH_2$
181	H	m=o=O	H				$CONH_2$
182	Ph	CH_2O	H				$CONH_2$
183	2-Py	CH_2O	H				H
184		CH_2O	H				$CONH_2$

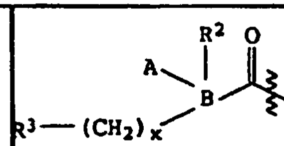
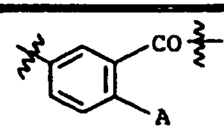
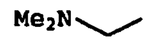
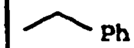
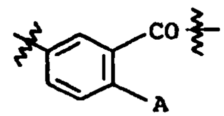
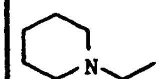
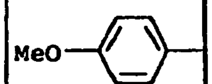
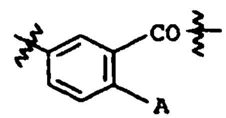
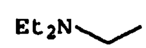
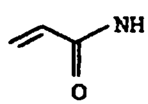
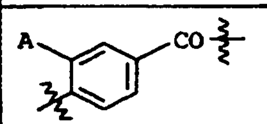
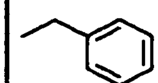
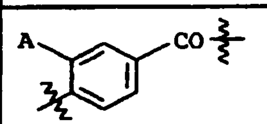
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
185	Ph	CONH	H				$CONH_2$
186	Naphth	CONH	H				H
187	Ph		H				H
188	3-Py	CH_2O	H				H
189	3-Tol	CH_2O	H				H

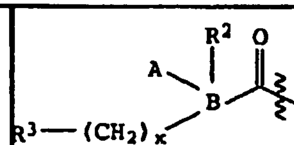
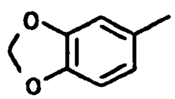
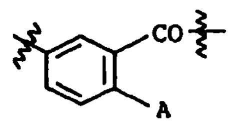
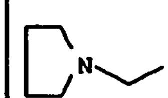
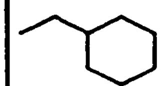
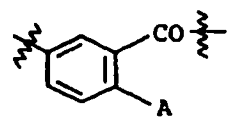
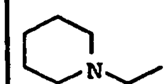
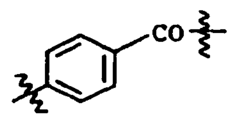
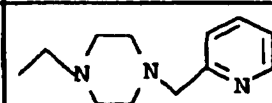
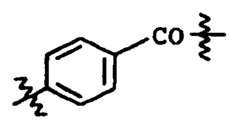
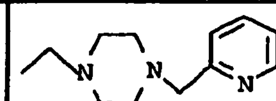
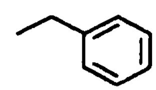
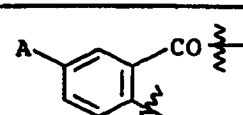
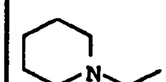
No.	R1	A	R2		R3—(CH2)x—	R4	R5
190	4-Py	CH_2O	H				$CONH_2$
191	2-Tol	CH_2O	H				$CONH_2$
192		CH_2O	H				H
193	H	m=o=O	H				H
194	Ph	CONH	H				$CONH_2$

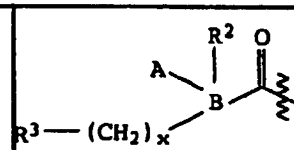
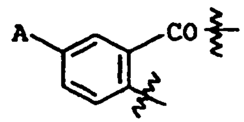
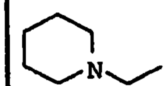
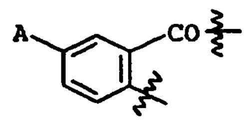
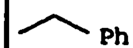
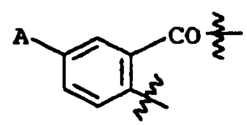
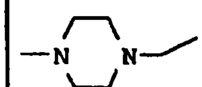
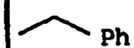
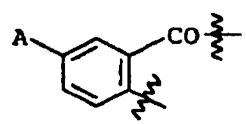
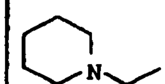
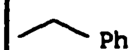
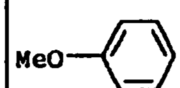
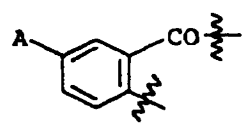
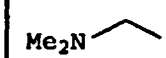
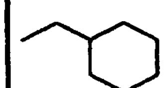
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
195	Naphth	CONH	H				$CONH_2$
196	H	m=o=O	H				$CONH_2$
197	2-Py	CH_2O	H				H
198	3-Py	CH_2O	H				$CONH_2$
199	3-Tol	CH_2O	H				$CONH_2$

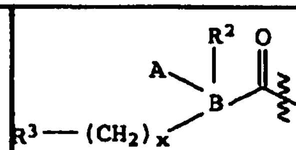
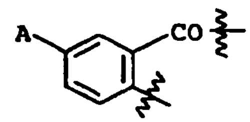
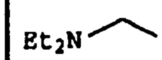
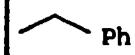
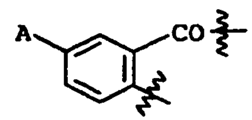
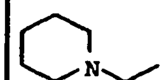
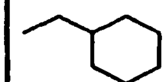
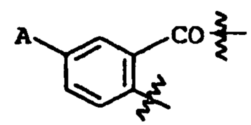
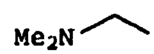
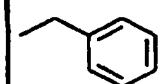
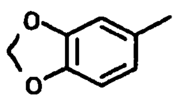
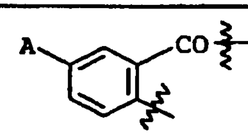
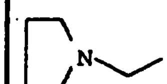
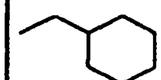
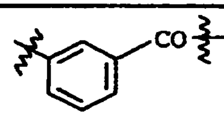
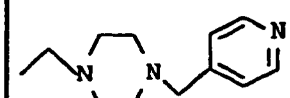
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
200	Ph	CH_2O	H				H
201		CH_2O	H				$CONH_2$
202	4-Py	CH_2O	H				H
203		CH_2O	H				$CONH_2$
204	2-Py	CH_2O	H				$CONH_2$

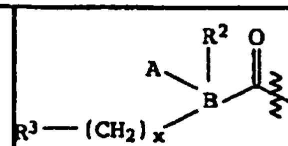
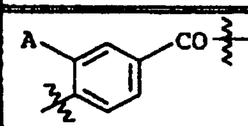
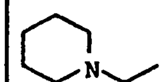
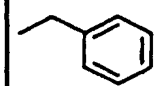
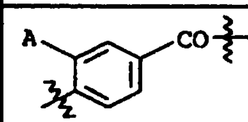
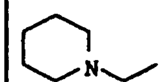
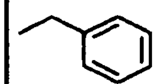
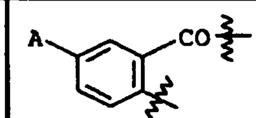
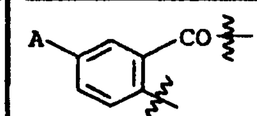
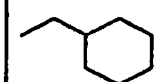
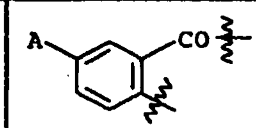
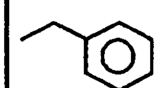
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
205	Ph	CH_2O	H				H
206	2-Py	CH_2O	H				$CONH_2$
207	2-Tol	CH_2O	H				H
208	Ph	CONH	H				H
209	Naphth	CONH	H				$CONH_2$

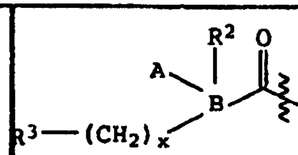
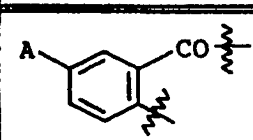
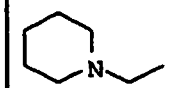
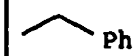
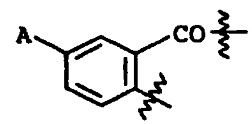
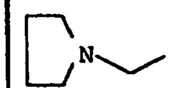
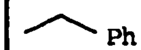
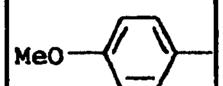
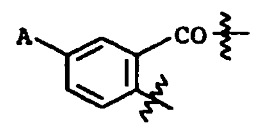
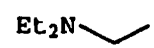
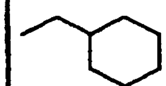
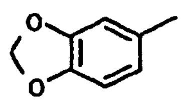
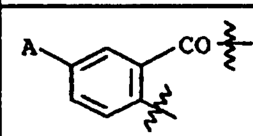
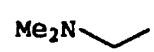
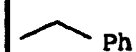
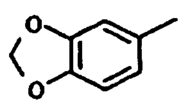
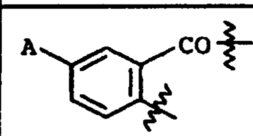
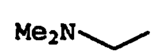
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
210	3-Py	CH_2O	H				H
211	4-Py	CH_2O	H				H
212		CH_2O	H				$CONH_2$
213	Ph		H				$CONH_2$
214	Ph	CONH	H				$CONH_2$

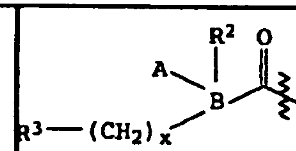
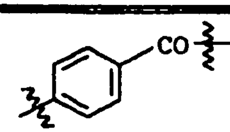
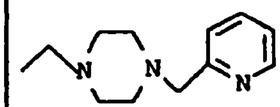
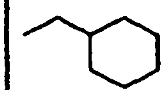
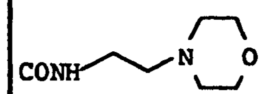
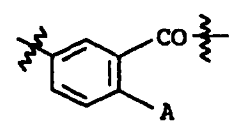
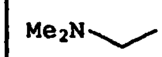
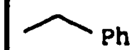
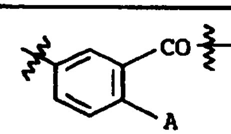
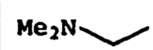
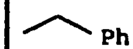
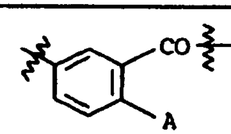
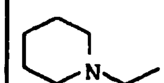
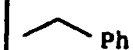
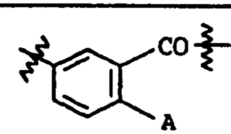
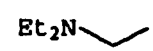
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
215		CH_2O	H				$CONH_2$
216	3-Tol	CH_2O	H				H
217	H	m=o=O	H				$CONH_2$
218	H	m=o=O	H				H
219	2-Py	CH_2O	H				H

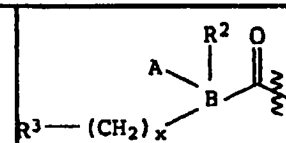
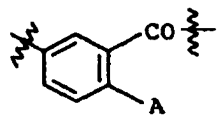
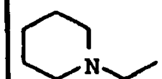
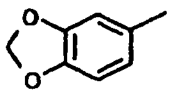
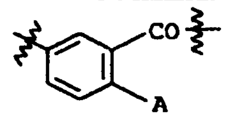
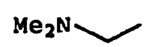
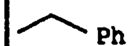
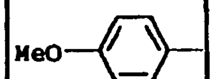
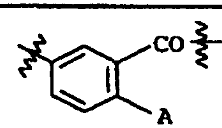
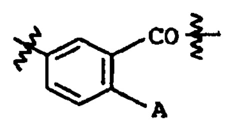
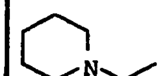
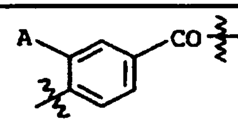
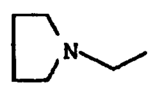
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
220	3-Py	CH_2O	H				H
221	2-Tol	CH_2O	H				$CONH_2$
222	4-Tol	CH_2O	H				$CONH_2$
223	4-Py	CH_2O	H				$CONH_2$
224		CH_2O	H				H

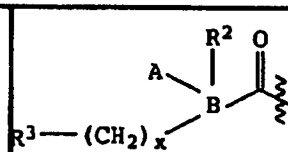
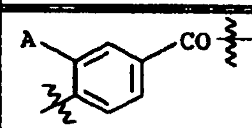
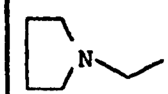
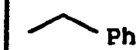
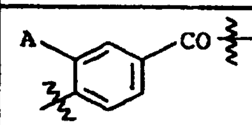
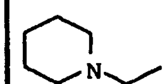
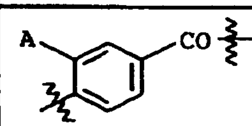
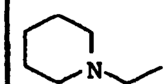
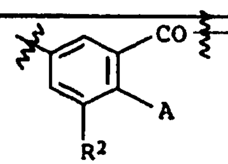
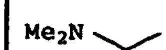
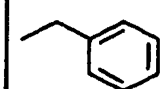
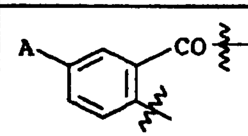
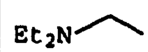
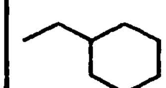
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
225	4-Py	CH_2O	H				H
226	Ph	CH_2O	H				$CONH_2$
227	3-Tol	CH_2O	H				H
228		CH_2O	H				H
229	H	m=o=O	H				$CONH_2$

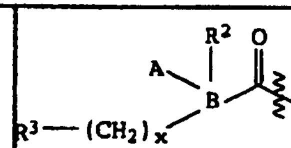
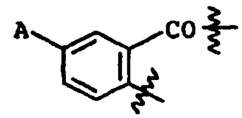
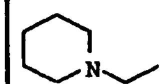
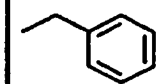
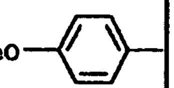
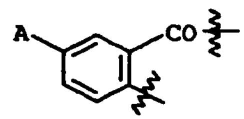
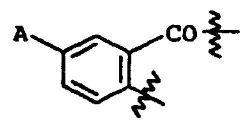
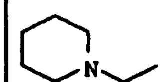
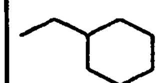
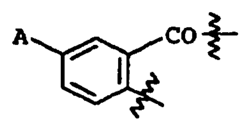
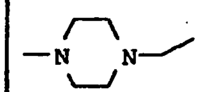
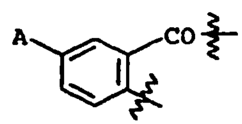
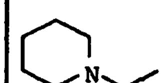
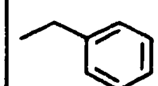
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
230	Ph	CONH	H				$CONH_2$
231	Naphth	CONH	H				$CONH_2$
232	2-Tol	CH_2O	H		Et_2N		H
233	2-Tol	CH_2O	H		Et_2N		$CONH_2$
234	3-Py	CH_2O	H		Me_2N		H

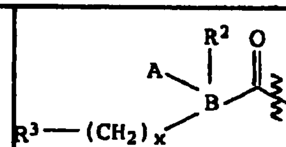
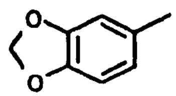
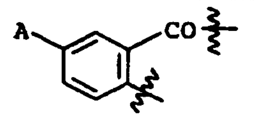
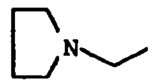
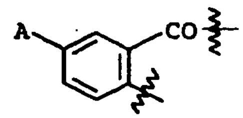
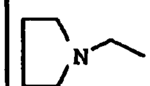
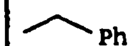
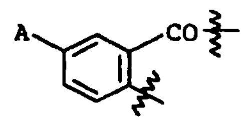
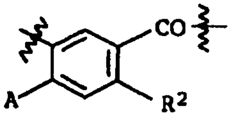
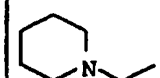
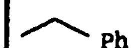
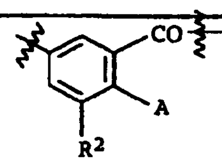
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
235	Ph	CH_2O	H				$CONH_2$
236		CH_2O	H				H
237		CH_2O	H				H
238		CH_2O	H				H
239		CH_2O	H				$CONH_2$

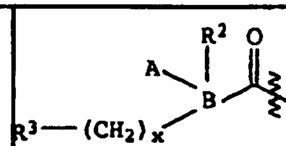
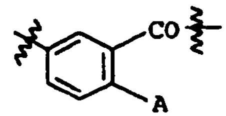
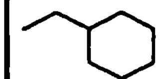
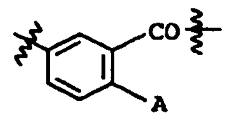
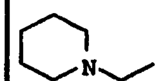
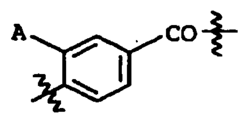
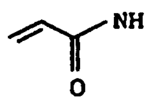
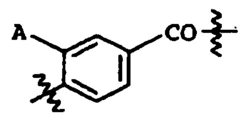
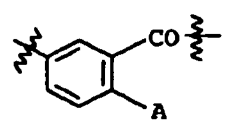
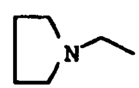
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
240	H	m=o=O	H				
241	Ph	CH_2O	H				H
242	3-Py	CH_2O	H				$CONH_2$
243	4-Py	CH_2O	H				H
244	2-Tol	CH_2O	H				H

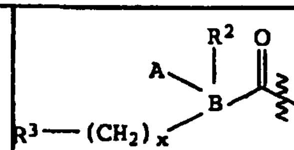
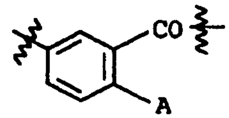
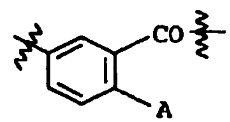
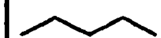
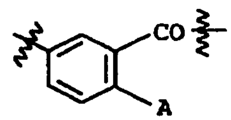
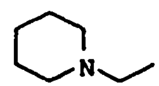
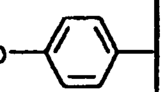
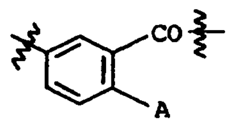
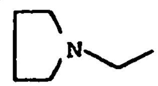
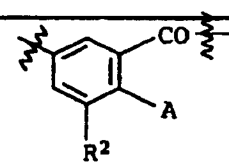
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
245	3-Tol	CH_2O	H				$CONH_2$
246		CH_2O	H				H
247		CH_2O	H				H
248	2-Py	CH_2O	H				$CONH_2$
249	Ph	CONH	H				H

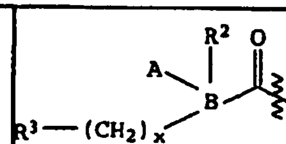
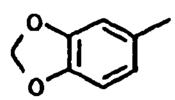
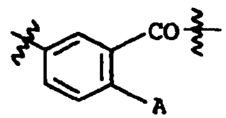
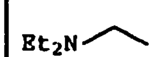
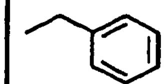
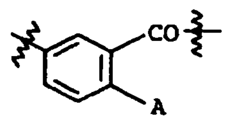
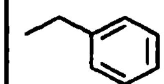
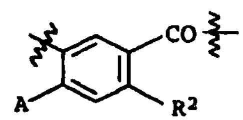
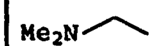
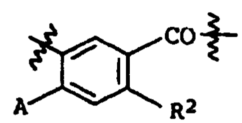
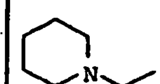
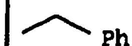
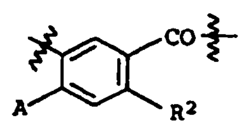
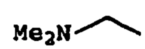
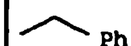
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
250	Ph	CONH	H				$CONH_2$
251	Ph	CONH	H				H
252	Naphth	CONH	H				H
253	Ph	SO_2NH	Et				H
254	Ph	CH_2O	H				H

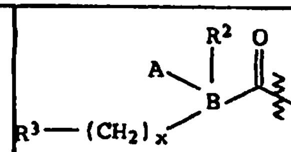
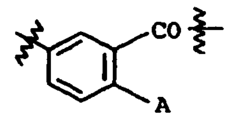
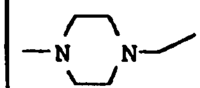
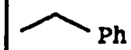
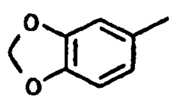
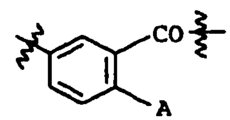
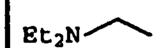
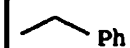
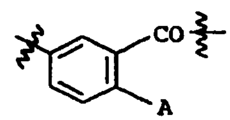
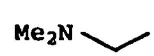
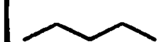
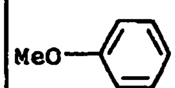
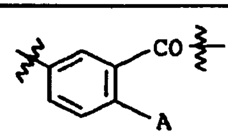
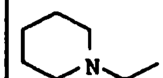
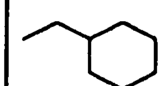
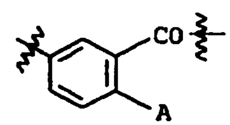
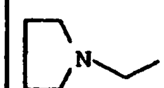
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
255	2-Py	CH_2O	H				$CONH_2$
256	MeO	CH_2O	H		Me_2N		H
257	3-Py	CH_2O	H				$CONH_2$
258	2-Tol	CH_2O	H			Ph	$CONH_2$
259	3-Tol	CH_2O	H				$CONH_2$

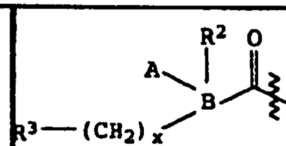
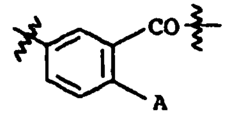
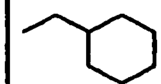
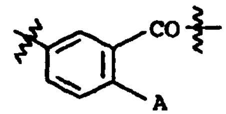
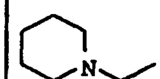
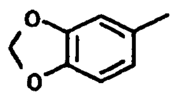
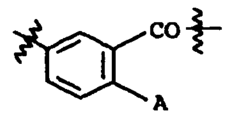
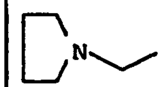
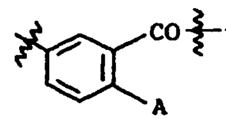
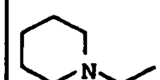
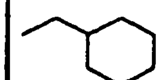
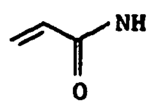
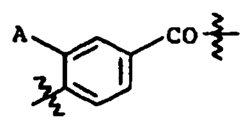
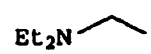
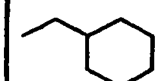
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
260		CH_2O	H				H
261	4-Py	CH_2O	H				$CONH_2$
262	Ph	CH_2O	H				H
263	Bu	SO_2NH	MeO				H
264	Naphth	SO_2NH	Et				H

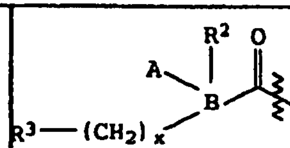
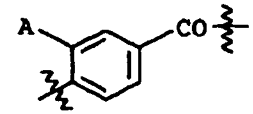
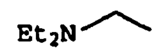
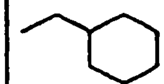
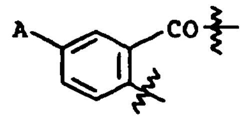
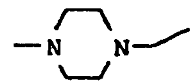
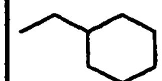
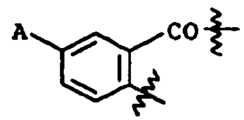
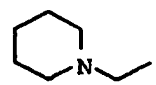
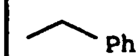
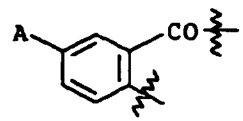
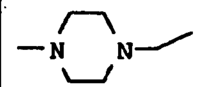
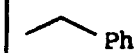
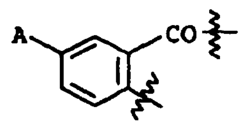
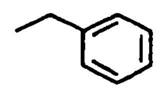
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
265	4-Py	CH_2O	H				$CONH_2$
266	3-Tol	CH_2O	H				H
267	Ph	CONH	H				$CONH_2$
268	Ph		H				$CONH_2$
269	2-Py	CH_2O	H				$CONH_2$

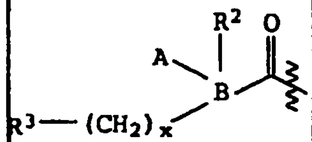
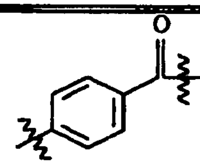
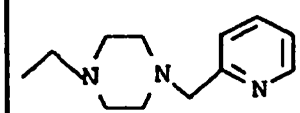
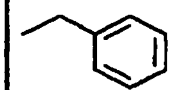
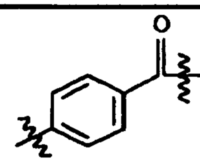
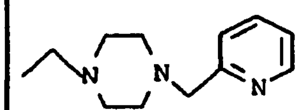
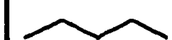
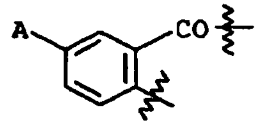
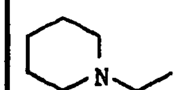
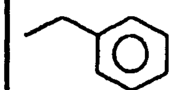
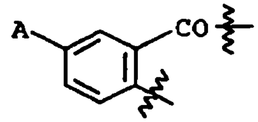
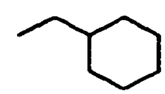
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
270	2-Tol	CH_2O	H		Et_2N 	 Ph	$CONH_2$
271	Ph	CH_2O	H		Me_2N 		H
272	3-Py	CH_2O	H			 Ph	$CONH_2$
273	MeO 	CH_2O	H			 Ph	$CONH_2$
274	Ph	SO_2NH	Et		Et_2N 	 Ph	H

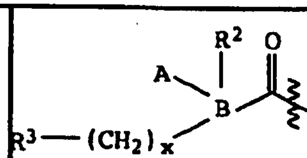
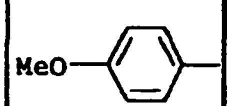
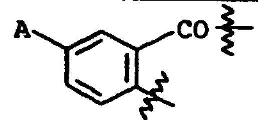
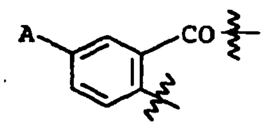
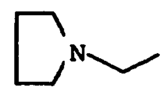
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
275		CH_2O	H				$CONH_2$
276	Naphth	SO_2NH	Et				$CONH_2$
277	Ph	SO_2NH	MeO				H
278	Naphth	SO_2NH	MeO				H
279	Bu	SO_2NH	MeO				H

No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
280	Ph	CH_2O	H				$CONH_2$
281		CH_2O	H				H
282	Ph	CH_2O	H				$CONH_2$
283		CH_2O	H				H
284	2-Py	CH_2O	H				H

No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
285	2-Py	CH_2O	H				$CONH_2$
286	3-Py	CH_2O	H			 Ph	H
287		CH_2O	H			 Ph	$CONH_2$
288	2-Tol	CH_2O	H				H
289	Ph		H				$CONH_2$

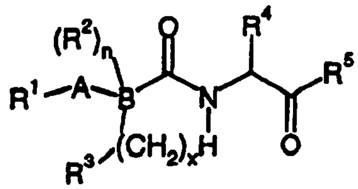
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
290	Ph	CONH	H				$CONH_2$
291	4-Py	CH_2O	H				H
292	4-Py	CH_2O	H				$CONH_2$
293	3-Tol	CH_2O	H				$CONH_2$
294	2-Tol	CH_2O	H				$CONH_2$

No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
295	H	m=o=O	H				H
296	H	m=o=O	H				H
297	3-Tol	CH_2O	H				H
298	2-Py	CH_2O	H				H

No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
299		CH_2O	H				$CONH_2$
298	2-Tol	CH_2O	H				H

We claim:

1. An amide of the formula I

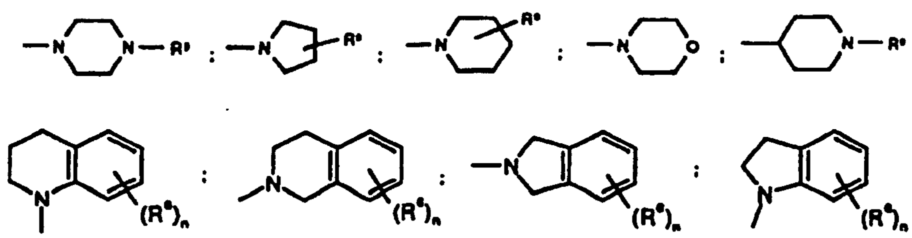


and its tautomeric and isomeric forms, possible enantiomeric and diastereomeric forms, and possible physiologically tolerated salts, in which the variables have the following meanings:

R^1 can be hydrogen, C_1-C_6-alkyl, branched and unbranched, phenyl, naphthyl, quinolyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, quinazolyl, quinoxalyl, thienyl, benzothienyl, benzofuranyl, furanyl and indolyl, it being possible for the rings also to be substituted by to 3 R^6 radicals, and

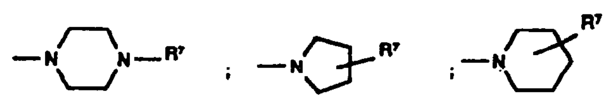
R^2 are hydrogen, C_1-C_6-alkyl, branched or unbranched, O-C_1-C_6-alkyl, branched or unbranched, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyl-phenyl, C_2-C_6-alkenyl-phenyl, C_2-C_6-alkynyl-phenyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, NHCO-C_1-C_4-alkyl, NHCO-phenyl, $CONHR^9$, $NHSO_2$-C_1-C_4-alkyl, $NHSO_2$-phenyl, SO_2-C_1-C_4-alkyl and SO_2-phenyl, and

R^3 can be NR^7R^8 or a ring such as



R^4 is $-C_1$-C_6-alkyl, branched or unbranched, which may also carry a phenyl, pyridyl, thienyl, cyclohexyl, indolyl or naphthyl ring which is in turn substituted by a maximum of two R^6 radicals, and

R^5 is hydrogen, $COOR^{11}$ and CO-Z in which Z is $NR^{12}R^{13}$ and

 and

R^6 is hydrogen, C_1-C_4-alkyl, branched or unbranched, $-O-C_1$-C_4-alkyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, -NHCO-C_1-C_4-alkyl, -NHCO-phenyl, $-NHSO_2$-C_1-C_4-alkyl, $-NHSO_2$-phenyl, $-SO_2$-C_1-C_4-alkyl and $-SO_2$-phenyl, and

R^7 is hydrogen, C_1-C_6-alkyl, linear or branched, and which may be substituted by a phenyl ring which itself may also be substituted by one or two R^{10} radicals, and

R^8 is hydrogen, C_1-C_6-alkyl, linear or branched, which may be substituted by a phenyl ring which may itself also be substituted by one or two R^{10} radicals, and

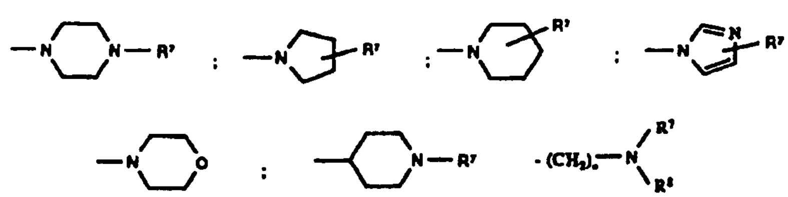
R^9 is hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a sub-

stituent R^{16}, or phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, naphthyl, quinolyl, imidazolyl, which may also carry one or two substituents R^{14}, and

R^{10} can be hydrogen, C_1-C_4-alkyl, branched or unbranched, -O-C_1-C_4-alkyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, -NHCO-C_1-C_4-alkyl, -NHCO-phenyl, -$NHSO_2$-C_1-C_4-alkyl, -$NHSO_2$-phenyl, -SO_2-C_1-C_4-alkyl and -SO_2-phenyl

R^{11} is hydrogen, C_1-C_6-alkyl, linear or branched, and which may be substituted by a phenyl ring which may itself also be substituted by one or two R^{10} radicals, and

R^{12} is hydrogen, C_1-C_6-alkyl, branched and unbranched, and



[sic]

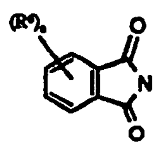
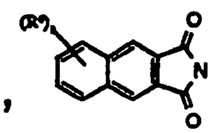
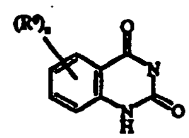
R^{13} is hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also be substituted by a phenyl ring which may also carry an R^{10} radical, and by [lacuna]
and

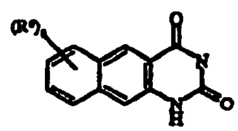
R^{14} is hydrogen, C_1-C_6-alkyl, branched or unbranched, O-C_1-C_6-alkyl, branched or unbranched, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, or two R^{14} radicals may represent a bridge $OC(R^{15})_2O$, and

R^{15} is hydrogen, C_1-C_6-alkyl, branched and unbranched, and

R^{16} can be a phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, pyrrolyl, naphthyl, quinolyl, imidazolyl ring, which may also carry one or two substituents R^6, and

A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-(CH_2)_o-SO-(CH_2)_m-$, $-(CH_2)_o-SO_2-(CH_2)_m-$, $-CH{=}CH-$, $-C{\equiv}C-$, $-CO-CH{=}CH-$, $-(CH_2)_o-CO-(CH_2)_m-$, $-(CH_2)_m-NHCO-(CH_2)_o-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-NHSO_2-(CH_2)_o-$, $-NH-CO-CH{=}CH-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$, $-CH{=}CH-CONH-$ and


,

,

and


[sic]

R^1-A together are also [lacuna] and

B is phenyl, pyridine, pyrimidine, pyrazine, imidazole and thiazole, and

x is 1, 2 or 3, and

n is a number 0, 1 or 2, and

m, o is, independently of one another, a number 0, 1, 2, 3 or 4.

2. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B is pyridine or phenyl, and

R^5 is hydrogen, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which [lacuna] also carry a substituent R^{16},

R^{16} phenyl which may also carry one or two substituents R^{14}, and

n 0 and 1, and

x 1.

3. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B is pyridine or phenyl, and

R^5 is $CONR^{12}R^{13}$, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which [lacuna] also carry a substituent R^{16},

R^{16} phenyl which may also carry one or two substituents R^{14}, and

n 0 and 1, and

x 1.

4. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where
B is pyridine or phenyl, and

R^2 is hydrogen

R^5 is hydrogen, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which [lacuna] also carry a substituent R^{16},

R^{16} phenyl which may also carry one or two substituents R^{14}, and

n 0 and 1, and

x 1.

5. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B is pyridine or phenyl, and

R^2 is hydrogen

R^5 is $CONR^{12}R^{13}$, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which [lacuna] also carry a substituent R^{16},

R^{16} phenyl which may also carry one or two substituents R^{14}, and

n 0 and 1, and

x 1.

6. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$,

$-(CH_2)_m-CONH-(CH_2)_o-$,
$-(CH_2)_m-SO_2NH-(CH_2)_o-$, and

B is pyridine or phenyl, and

R^2 is hydrogen, and

R^5 is hydrogen, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a substituent R^{16}, and

R^{16} phenyl, and

m, n, o 0 and 1, and

x 1.

7. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-CH{=}CH-$, $-C{\equiv}C-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$, and

B is pyridine or phenyl, and

R^2 is hydrogen

R^5 is $CONR^{12}R^{13}$, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a substituent R^{16}, and

R^{16} phenyl, and

m, n, o	0 and 1, and
x	1.

8. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B	is pyridine or phenyl, and
R^1, R^2	are hydrogen, and
R^5	is hydrogen, and
R^9	hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a substituent R^{16}, and
R^{16}	phenyl, and
m, n, o	0, and
x	1.

9. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B	is pyridine or phenyl, and
R^1, R^2	are hydrogen
R^5	is $CONR^{12}R^{13}$, and
R^9	hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a substituent R^{16}, and
R^{16}	phenyl, and

m, n, o 0

x 1.

10. The use of amides of the formula I as claimed in claims 1-5 for treating diseases.

11. The use of amides of the formula I as claimed in claims 1-5 as inhibitors of cysteine proteases.

12. The use as claimed in claim 6 as inhibitors of cysteine proteases such as calpains and cathepsins, in particular calpains I and II and cathepsins B and L.

13. The use of amides of the formula I as claimed in claims 1-5 for production as pharmaceuticals for treating diseases in which elevated calpain activities occur.

14. The use of amides of the formula I as claimed in claims 1-5 for producing pharmaceuticals for treating neurodegenerative disorders and neuronal damage.

15. The use as claimed in claim 9 for treating neurodegenerative disorders and neuronal damage induced by ischemia, trauma or massive bleeding.

16. The use as claimed in claim 10 for treating stroke and craniocerebral trauma.

17. The use as claimed in claim 10 for treating Alzheimer's disease and Huntington's disease.

18. The use as claimed in claim 10 for treating epilepsies.

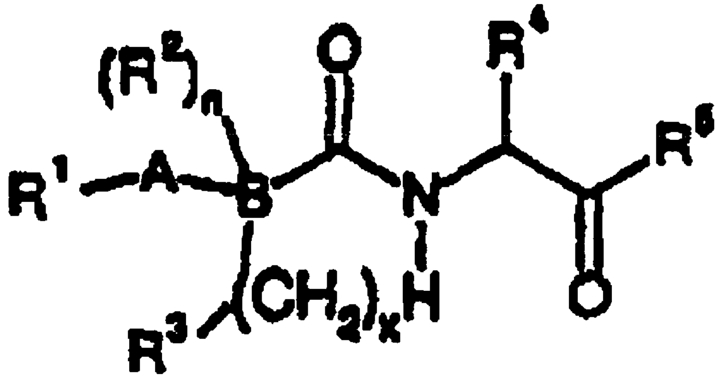
19. The use of compounds of the formula I as claimed in claims 1-5 for producing pharmaceuticals and [sic] treating damage to the heart after cardiac ischemias, damage to the kidneys after renal ischemias, skeletal muscle damage, muscular dystrophies, damage produced by proliferation of smooth muscle cells, coronary vasospasm, cerebral vasospasm, cataracts of the eyes and restenosis of blood vessels after angioplasty.

20. The use of amides of the formula I as claimed in claims 1-5 for producing pharmaceuticals for treating tumors and metastasis thereof.

21. The use of amides of the formula I as claimed in claims 1-5 for producing pharmaceuticals for treating disorders in which elevated interleukin-1 levels occur.

22. The use of amides according to claims 1-5 for treating immunological disorders such as inflammations and rheumatic disorders.

23. A pharmaceutical preparation for oral, parenteral or intraperitoneal use, comprising at least one amide I as claimed in claims 1-5 per single dose, besides conventional pharmaceutical ancillary substances.



(I)